Physio-psycho-social interaction mechanism in dyadic health of young and middle-aged stroke survivors and their spousal caregivers: a longitudinal observational study protocol

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ABSTRACT

Introduction In recent years, stroke has become more common among young people. Stroke not only has a profound impact on patients’ health but also incurs stress and health threats to their caregivers, especially spousal caregivers. Moreover, the health of stroke survivors and their caregivers is interdependent. To our knowledge, no study has explored dyadic health of young and middle-aged stroke survivors and their spousal caregivers from physiological, psychological and social perspectives. Therefore, this proposed study aims to explore the mechanism of how physiological, psychological and social factors affect dyadic health of young and middle-aged stroke survivors and their spousal caregivers. The findings of this study will provide implications for developing interventions to improve dyadic health of this growing population.

Methods and analyses We will collect data from 57 dyads of young and middle-aged stroke survivors and their spousal caregivers during hospitalisation and at 1, 3, 6, 9 and 12 months after discharge. Questionnaires will be used to collect participants’ demographic information, stress, depression, anxiety, benefit finding, social support, mutuality and quality of life. The following physiological reactions will be collected at baseline, including interleukin 6, tumour necrosis factor-alpha and salivary cortisol.

Ethics and dissemination The study was approved by the ethics review committee of life sciences of Zhengzhou University (No. ZZUIRB2020-53). Prior to being enrolled in the study, participants will be given full and detailed information about the possible risks involved, the informed consent process, confidentiality, the study procedure and secure data storage. Participants will be guaranteed that they can withdraw from the study at any time without providing a reason or leading to any consequences. Both oral and written informed consent will be obtained from all participants. The findings of this proposed study will be disseminated through peer-reviewed journals and academic conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be the first longitudinal study on the dyadic health mechanism in young and middle-aged stroke survivors and their spousal caregivers.
⇒ This study will be the first study to consider the interaction mechanism of dyadic health from physiological, psychological and social perspectives.
⇒ This study will be the first study to include physiological reactions of dyadic health of young and middle-aged stroke survivors and their spousal caregivers.
⇒ In this study, physiological reactions will only be collected at baseline; thus, we will not be able to examine the relationship between changes in physiological reactions and dyadic health.

INTRODUCTION

Stroke has become a leading cause of death and disability worldwide. In China, the lifetime risk of stroke was 39.3%, ranking the first in the world. In recent years, stroke has become more common among young people. The incidence of ischaemic stroke in young and middle-aged people aged 18–50 years has increased by 40% worldwide, which has seriously threatened health of the primary labour force. Studies have found that 75%–80% of stroke survivors have some kind of dysfunction. Stroke-related complications may continue to affect survivors, especially those who are young and middle-aged because their life cycle is significantly longer than that of older survivors. Moreover, compared with older survivors, young and middle-aged survivors have a greater risk of experiencing negative emotions associated with stroke.

Stroke not only has a profound impact on patients’ health but also incurs stress on their caregivers, especially spousal caregivers.
leading to their diminished quality of life, anxiety and depression. These outcomes, in turn, compromise spousal caregivers’ ability to provide quality long-term care to stroke survivors. Moreover, the health of stroke survivors and their spousal caregivers affects each other and thus is interdependent. If patients who had a stroke suffer from anxiety and depression, their caregivers are also more likely to experience their symptoms. In addition, there is an actor–partner effect between depression and quality of life in stroke survivors and their caregivers. This suggests that we need to study stroke survivors and their caregivers together. Although many researchers have noticed this need, the interaction mechanism of dyadic health of stroke survivors and their spousal caregivers is unclear, and most studies used the self-report method to assess their dyadic health. It is particularly important to include objective measures to analyse the mechanism of dyadic health. Studies have found that excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis and abnormal expression of inflammatory cytokines (interleukin 6 (IL-6), tumour necrosis factor-alpha (TNF-α)) may explain the relationship between physical health and mental health. Therefore, we propose a longitudinal observational study to explore the interaction mechanism of dyadic health in young and middle-aged stroke survivors and their spousal caregivers.

Background

Theoretical framework

As early as the 1970s, Engel proposed a biopsychosocial medical model, emphasising that disease and health are influenced by bio-psycho-social factors. The dyadic illness management theory also proposes that dyadic health refers to the physiological, psychological and social health status of both stroke survivors and their caregivers and that the two’s health is inseparable, interacting with each other and changing together. However, there is no detailed elucidation of how physio-psycho-social factors are intertwined. The Pittsburgh Mind-Body Center Model believes that patients’ disease characteristics and caregivers’ characteristics can lead to psychological changes in caregivers, such as anxiety, depression and stress. These psychological reactions can then affect caregivers’ physiological responses and, ultimately, their physical health. Shaffer proposed the interdependent biopsychosocial model of patients’ and caregivers’ physical morbidity development. He argues that by living in a common environment, patients and caregivers experience the same physio-psycho-behavioural response, which interacts with psychological distress and ultimately affects partners’ physiological responses and health outcomes. The stress-buffering model suggests that social support has a buffering effect on stress, thus promoting individuals’ physical and mental health. Based on the

Figure 1  The conceptual framework of this study. Illness stimulates stress among stroke survivors and their caregivers. Stress then impacts their dyadic health indirectly or directly by activating physiological and psychological responses. These responses then interact with psychological responses. Furthermore, social support and mutuality buffer the relationship between stress and health. Double-headed arrows mean bi-directional relationship. IL-6, interleukin 6; SF-12, 12-item Short-Form Health Survey; TNF-α, tumour necrosis factor-alpha.
above theories, a theoretical framework for this study was developed (figure 1). Based on this framework, stroke can induce stress on stroke survivors and their spousal caregivers. This stress can cause psychological (negative or positive) and physical (HPA axis and inflammatory factors) reactions, ultimately affecting stroke survivors’ and spousal caregivers’ mental and physical health. However, social factors (social support and mutuality) regulate the relationships among these factors.

Physiological factors and dyadic health
Salivary cortisol is widely known as a biomarker for stress. Under stress, the HPA axis is activated, and cortisol enters saliva as the final hormone product. A flatter diurnal cortisol slope (DCS) is a proposed mechanism to explain the link between psychosocial stress and various health outcomes. A flat DCS, a blunted cortisol arousal response (CAR) and elevated nocturnal cortisol are significantly associated with adverse psychosocial outcomes. Nightingale et al. also found that a flat DCS is associated with increased care burden and poor quality of life in caregivers of patients with head and neck cancer. Hsiao et al. found a positive correlation between DCS of patients with breast cancer and that of their spouses.

Inflammatory cytokines (eg, IL-6 and TNF-α) are important in maintaining health. Stress can threaten a person’s health through its interactions with inflammatory factors and the HPA axis. A study revealed that the expression of IL-6 and TNF-α in stroke survivors with depression was significantly higher than that in those without depression, suggesting that IL-6 and TNF-α may be a latent physiological mechanism explaining the development of poststroke depression. TNF-α was also found to affect quality of life in patients with breast cancer and interact with depression in its pathway of affecting quality of life. In addition, inflammatory markers are significantly associated with caregiving distress. IL-6 in caregivers was found to be related to fatigue and days of care provided per week. TNF-α in caregivers was found to be associated with depression, fatigue and days of care provided per week. However, there are no studies on the interaction between physiological responses and psychosocial factors in young and middle-aged stroke survivors and their spousal caregivers.

Psychological factors and dyadic health
Increasing evidence shows that psychological conditions of stroke survivors and their caregivers are inextricably linked to their dyadic health. Illness is a sudden life-stress event for both stroke survivors and caregivers and poses a serious threat to their health. Stress is an alarm from the body triggered by illness. Perceived stress has a significant impact on depression and anxiety. Poststroke anxiety and depression are common in stroke survivors and their spousal caregivers. These negative emotions not only compromise their quality of life but also increase the risk of mortality.

At the same time, with the development of positive psychology, many studies have found that patients and their caregivers obtain many benefits during illness and their care. This study calls this phenomenon ‘benefit finding’, which coexists with negative emotions. Benefit finding not only improves quality of life but also reduces anxiety and depression.

Social factors and dyadic health
In addition, dyadic health is affected by social factors such as social support and intimacy with partners. The Stress-Buffering model indicates that positive social support plays a buffering role between stress and health and directly and indirectly affects a person’s health. Research has shown that social support positively affects mental health and quality of life. Intimacy with partners is another social factor that influences dyadic health. Caregivers serve as the primary source of support for stroke survivors; thus, the relationship between the two is important for each other’s physical and mental health.

In summary, stroke has a profound impact on physical and mental health of stroke survivors and their spousal caregivers. However, at present, there is no clear conclusion on the dyadic health mechanism of young and middle-aged stroke survivors and spousal caregivers. Biopsychosocial medical models provide a novel approach to this issue.

Objectives
The purpose of this study is to explore how physiological, psychological and social factors affect dyadic health of young and middle-aged stroke survivors and their spousal caregivers. The specific hypotheses are as follows:

- Physiological, psychological and social factors significantly affect quality of life of stroke survivors and their spousal caregivers.
- Physiological (IL-6, TNF-α and salivary cortisol) and psychological reactions (depression, anxiety and benefit finding) mediate the relationship between dyadic stress and dyadic quality of life.
- Social reactions (social support and mutuality) moderate the relationships among dyadic stress, physiological reactions (IL-6, TNF-α and salivary cortisol) and psychological reactions (depression, anxiety and benefit finding) and dyadic quality of life.

METHODS AND ANALYSIS
Design
A longitudinal observational design will be adopted. Stroke survivors and their spousal caregivers from the Neurology Department of the Second Affiliated Hospital of Zhengzhou University and Luohe Central Hospital will be recruited and followed up for 12 months post-discharge. The proposed recruitment start date was in June 2022, and the proposed follow-up end date is in December 2023.
Participants
Convenience sampling will be used to recruit young and middle-aged stroke survivors and their spousal caregivers. Researchers will work together with neurologists, charge nurses and nurses to recruit participants. Recruitment strategies included project presentations and flyers at physicians’ offices and patients’ rooms. Stroke survivor participant inclusion criteria include people who (1) have a first-episode stroke based on the fourth national diagnostic criteria for cerebrovascular disease and are confirmed by CT or MRI or who met the 11th revision of the International Classification of Diseases codes, (2) age 18–59 years and (3) understand the questionnaire and can complete the survey independently or with the help of caregivers. Spousal caregiver participant inclusion criteria include people who (1) are stroke survivors’ spousal, (2) are the primary caregivers identified by stroke survivor participants and (3) are 18 years and older. Exclusion criteria for stroke survivors and spousal caregivers include people who (1) have other serious chronic diseases such as a malignant tumour, heart failure, renal failure or respiratory failure, (2) have autoimmune system diseases, and/or are taking immunomodulatory medication, (3) are taking anti-inflammatory drugs and/or glucocorticoids, (4) are taking drugs that affect cognitive function such as antipsychotics, opioids and sedative-hypnotics or (5) have gingival bleeding or oral ulcer.

Sample size
G*Power was used to calculate the sample size. For analysis with repeated measurements, the effect was set at 0.25; α was set at 0.05; power was set at 80%. The number of measurements in this proposed study was six. According to the preliminary calculation, 40 dyads of participants will be needed. Allowing 10% invalid questionnaire and 30% attrition rate, 57 dyads of young and middle-aged stroke survivors and their caregivers will be needed for recruitment.

Data collection
Data will be collected at baseline and 1, 3, 6, 9 and 12 months after discharge (figure 2). The measurement time schedule is consistent with that in the dyadic longitudinal study of stroke at home and abroad. The baseline questionnaire will be collected by researchers face-to-face in the ward, and the follow-up questionnaire will be collected by researchers face-to-face at patients’ homes. Participants’ physiological reactions will be collected at baseline only by the responsible nurse in the ward. This is due to the fact that collecting physiological indicators during follow-up visits would be too resource-consuming for us. The following instruments will be used as measurements (table 1).

Patient-related predictors of dyadic health
A sociodemographic questionnaire will be used to collect stroke survivors’ information, including age, gender, education level, average monthly income, disease type and disease duration. The Barthel Index (BI) will be used to evaluate their functional status in activities of daily living. The BI contains ten activities of daily living. A higher score indicates more independence. A lower score indicates worse self-care ability and a higher degree of dependence. The BI has been widely used in stroke survivors with high internal consistency (Cronbach’s α=0.95).

The Chinese version of the Benefit Finding Scale consists of 22 items that assess patients’ perceived benefits from the disease. It has six subscales, including acceptance, family relations, personal growth, world view, social relations and health behaviours. The score of each item ranges from 1 point (none at all) to 5 points (very much). A higher score indicates more perceived positive changes.

Figure 2 The time flow of the study design.
The Cronbach’s alpha of the Chinese version of the scale was 0.95, showing high internal consistency.

Caregiver-related predictors of dyadic health
A sociodemographic questionnaire will be used to collect spousal caregivers’ information, including age, gender, education level, caregiving hours per day and caregiving duration. The Caregiver Benefit Finding Scale will be used to measure benefit finding among spousal caregivers. It has 26 items and six domains, including self-growth, health promotion, family growth and self-sublimation. The score for each item ranges from 1 to 5, representing the extent of agreement with this item. A higher score indicates more perceived benefit. The internal consistency of the scale in Chinese stroke caregivers has been verified with the Cronbach’s alpha ranging from 0.885 to 0.953.

Dyad-related predictors of dyadic health
The stress levels of young and middle-aged stroke survivors and spousal caregivers will be measured by the perceived stress scale (PSS-14). It has 14 items and measures two components of stress, including a sense of uncontrollability and a sense of nervousness. The score of each item ranges from 1 point (never) to 5 points (always). A higher score indicates more stress. The internal consistency of the PSS-14 was 0.84–0.86. The Chinese version of the PSS-14 has been shown to have high internal consistency (Cronbach’s α=0.90).

The degree of depression of dyads will be measured by the Patient Health Questionnaire 9-item version (PHQ-9). The response is a 4-point Likert scale, with a score of 4 or less indicating minimal depression, 5–9 indicating mild depression, 10–14 indicating moderate depression, 15–19 indicating moderately severe depression and 20 or more indicating severe depression. Based on a meta-analysis, the PHQ-9 is an optimal measure of depression in stroke survivors with a sensitivity of 0.86 and specificity of 0.79.

The degree of anxiety of dyads will be measured by the Generalised Anxiety Disorder 7-item version (GAD-7). The response is a 4-point Likert scale, with a score of 4 or less indicating no anxiety symptoms, 5–9 indicating

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**Table 1** Variables and instruments and time of assessment of this proposed study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Measured by</th>
<th>Individual measures</th>
<th>Postdischarge</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Stroke survivor</td>
<td>Spousal caregiver</td>
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<td>Patient-related predictors</td>
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<td>×</td>
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<tr>
<td>Demographic characteristics</td>
<td>Sociodemographic questionnaire</td>
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<td>×</td>
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<tr>
<td>Activities of daily life</td>
<td>BI</td>
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<td>×</td>
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<tr>
<td>Benefit finding</td>
<td>The Benefit Finding Scale</td>
<td>×</td>
<td>×</td>
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<tr>
<td>Caregiver-related predictors</td>
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<td>Demographic characteristics</td>
<td>Sociodemographic questionnaire</td>
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<tr>
<td>Benefit finding</td>
<td>The Caregiver Benefit Finding Scale</td>
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<tr>
<td>Dyad-related predictors</td>
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<tr>
<td>Stress</td>
<td>The Perceived Stress Scale</td>
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<tr>
<td>Depression</td>
<td>PHQ-9</td>
<td>×</td>
<td>×</td>
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<tr>
<td>Anxiety</td>
<td>GAD-7</td>
<td>×</td>
<td>×</td>
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<tr>
<td>Intimate relationship</td>
<td>Mutuality Scale</td>
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<tr>
<td>Health</td>
<td>SF-12</td>
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<td>×</td>
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<tr>
<td>Physiological reactions</td>
<td>IL-6, TNF-α, salivary cortisol</td>
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**Note:** BI, Barthel Index; GAD-7, Generalised Anxiety Disorder 7-item version; IL-6, interleukin 6; PHQ-9, Patient Health Questionnaire 9-item version; SF-12, 12-item Short-Form Health Survey; TNF-α, tumour necrosis factor alpha.
suspicious mild anxiety, 10–14 indicating suspicious medium anxiety and 15 or more indicating severe anxiety symptoms. The scale has good internal consistency (Cronbach’s α=0.92). This scale has been translated into Chinese and shown to have a Cronbach’s alpha of 0.84.3

Social support will be measured by the Perceived Social Support Scale. It has 12 items with three components, including family support, friends support and other support. Each item ranges from 1 point (strongly disagree) to 7 points (strongly agree). A higher score indicates more social support. The internal consistency of the scale was 0.88. This scale has been translated into Chinese and verified in stroke caregivers with a Cronbach’s alpha of 0.87.5

The mutuality levels of dyads will be measured by the Mutuality Scale. It has 14 items and four components, including love and affection, shared pleasurable activities, shared values and reciprocity. Each item ranges from 0 points (not at all) to 4 points (very much). A higher score indicates that dyads perceive higher mutuality. The Cronbach’s alpha was >0.90 in stroke survivors and caregivers.6

Health will be measured by the Short-Form 12-item Health Survey. It consists of two components—physical health component and mental health component. The physical component consists of four domains—physical functioning, role-physical, bodily pain and general health. The mental component includes four domains—vitality, social functioning, role-emotional and mental health. A higher score indicates that dyads are healthier. This scale has been verified in stroke survivors and showed good psychological characteristics. The Cronbach’s alpha for the physical and mental health components was 0.845 and 0.812, respectively. This scale has been translated into Chinese.6

Physiological reactions (serum IL-6, TNF-α and salivary cortisol) will be collected and measured using specific tools. Three millilitres of peripheral venous blood will be drawn between 06:00 and 07:00 using EDTA anticoagulant tubes. Before sending them to the laboratory, we will store the paired blood samples at 4°C. After the samples arrive at the laboratory, we will use a centrifuge to separate the serum. The speed is set at 3000 rpm for 15 min. Finally, the samples will be transferred to cryopreservation tubes and stored at −80°C until they are examined by ELISA.

Saliva will be collected by a unique unified saliva collection tube (SARSTEDT AG & Co. KG) at awakening, 30 min after and bedtime. Eating, smoking, drinking caffeinated/alcoholic beverages, tooth brushing and use of mouthwashes will be prohibited for 30 min prior to saliva collection. Participants will be instructed to put the swab into their mouths for 2 min without chewing. If no minimal amount of saliva is obtained, the swab will be left in the mouth for longer. Samples will be centrifuged, and the saliva sample will be stored at −80°C until assayed. Salivary cortisol will be measured using ELISA, and the CAR (the change in cortisol levels from awakening to 30 min after awakening) and DCS (the changing slope in cortisol levels from awakening to bedtime) will be calculated.

Data analysis plan
IBM SPSS V.25.0 and Amos V.24.0 software will be used for statistical analysis. For descriptive statistics, means (SD) for continuous data with normal distribution, medians (IQR) for non-normal continuous data, and frequency (percentages) for categorical data will be used. Relationships among physiological, psychological and social factors and time-varying dyadic quality of life will be assessed using mixed-effects regression model. Stroke survivors and their spousal caregivers will be analysed separately. Several covariates will be considered, including stroke survivors’ demographic characteristics (gender, education level, average monthly income, disease type and disease duration), BI and spousal caregivers’ demographic characteristics (education level, caregiving hours per day and caregiving duration). We will use unstructured covariance matrix and maximum likelihood estimation method.

Interdependence between stroke survivors and their caregivers will be analysed by the actor–partner interdependence model (APIM). For both members of the dyads, the effect of a person’s X (independent) variable on their own Y (dependent) variable is called ‘actor effect’. The effect of their partner’s X variable on a person’s Y variable is called ‘partner effect’. Furthermore, we will add mediators to APIM to explore the mediating effects of physiological reactions (IL-6, TNF-α and salivary cortisol) and psychological reactions (depression, anxiety and benefit finding) between dyadic stress and dyadic quality of life. We will add moderators to APIM to explore the moderating effects of social reactions (social support and mutuality) on the relationships between dyadic stress, physiological reactions (IL-6, TNF-α, salivary cortisol) and psychological reactions (depression, anxiety, benefit finding) and dyadic quality of life. For longitudinal data, we will explore the mediating effect of psychological reactions (depression, anxiety and benefit finding) and the moderating effect of social reactions (social support and mutuality) on the relationship between baseline physiological reactions (IL-6, TNF-α and salivary cortisol) and dyadic quality of life at different time points.

In our study, stroke survivors and their spousal are heterosexual couples, so we will analyse them according to distinguishable dyads. First, we will build a saturated model and evaluate effects of all variables. Second, the model will be simplified by adding constraint conditions. The optimal model will be selected according to χ², the comparative fit index ≥0.90, the standardised root-mean-square residual <0.08 and the root mean square error of approximation <0.06. Indirect effects will be estimated by a bootstrap procedure (5000 resamples) and a 95% CI. The missForest will be used to impute missing values.
Patient and public involvement
Patients, caregivers and/or the public are not involved in the design, conduct, reporting or dissemination of this study.

ETHICS AND DISSEMINATION
The study was approved by the ethics review committee of life sciences of Zhengzhou University (number: ZZUIRB2020-53). All the subjects participating in this study will be given full and detailed information about the possible risks involved, the informed consent process, confidentiality, study procedure and secure data storage. Both oral and written informed consent will be obtained from every participant. Participants are informed of their right to withdraw at any time during the study period. All samples were anonymous and only used for this study to ensure the confidentiality of the data. In addition, biological specimens will only be used for measuring the physiological reactions mentioned in the protocol and informed consent. The findings of this proposed study will be disseminated through peer-reviewed journals and academic conferences.

Contributors
YM, DX, BL and ZZ designed this study. DX drafted the manuscript with the help of YM and ZZ. SG, WW, YM, HL, SC and EG revised the manuscript critically. PZ and ZL made a significant contribution to the design of the data collection section. All authors approved the final version of the manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (grant number: 72004205), China Postdoctoral Science Foundation Project (grant number: 2019 M652558) and Key Research Projects of Higher Education Institutions of Henan (grant number: 21A320068).

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

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