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Effect of Long-term COVID-19 on the Female Reproductive System: A Literature Review

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Introduction

Long Covid arises in individuals previously infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), irrespective of whether they exhibited symptomatic or asymptomatic infection. This condition typically emerges around four weeks following recovery from the acute phase of the illness, persisting for weeks, months, and sometimes even years thereafter. Clinical diagnosis relies on a history of new, recurring, or ongoing health issues, often presenting with a perplexing array of symptoms and typically normal test results, leading to a delay in the diagnosis and management. The documented common symptoms of long-term COVID-19 are fatigue, insomnia, post-exertional malaise, cognitive dysfunction, and muscle aches [1].

While the precise mechanisms underlying Long Covid remain unknown, emerging evidence sheds light on the complex interplay between viral pathogenesis, immune dysregulation, and organ-specific sequelae. SARS-CoV-2 primarily affects the respiratory system, but it also directly and indirectly affects other organs, including the female reproductive system. It remains unclear whether these enduring effects stem directly from SARS-CoV-2 or result from the medications used to combat it [2].

Studies show that SARS-CoV-2 binds to angiotensin-converting enzyme receptor 2 (ACE2) which plays a major role in the renin-angiotensin-system (RAS). Within this system angiotensin I is converted into angiotensin II via ACE, and angiotensin 1-9 via ACE 2. Angiotensin II in turn takes three pathways: binding to angiotensin 1 receptor, leading to tissue injury; binding to angiotensin receptor 2, promoting tissue protection; and conversion to angiotensin 1-7 via ACE 2 also contributing to tissue protection, and thereby balancing the first pathway [3].

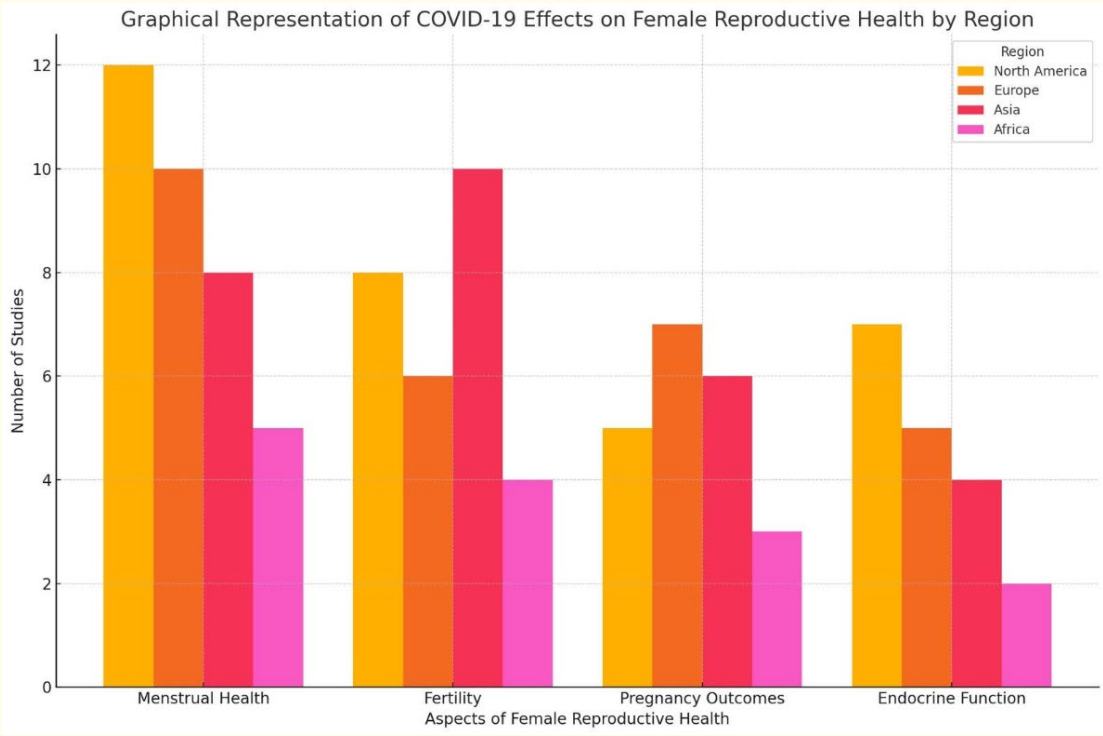
SARS-CoV-2's targeting of ACE2 disrupts this delicate balance, resulting in the accumulation of angiotensin I and II while decreasing levels of angiotensin 1-7. This disturbance impacts the equilibrium between tissue protection and injury. Angiotensin 1-7 plays an important role in the female reproductive system, supporting ovulation, maintaining endometrium during the ovulatory phase, and facilitating healthy placenta development. Therefore, a decrease in angiotensin 1-7 can lead to abnormal functions of the female reproductive system [3]. ACE2 receptors are also found in the hypothalamus, pituitary gland, adrenal glands, and other endocrine organs, leading to the effect of the endocrine system by SARS-CoV 2.

It has been demonstrated that SARS-CoV-2 alters the hypothalamic-pituitary axis, which may result in abnormalities in the release of gonadotropin-releasing hormone (GnRH) [4]. Follicle- stimulating hormone (FSH) and luteinizing hormone (LH) levels may change as a result, which may then affect ovarian function, regular menstruation, and fertility in general. These results highlight the necessity for additional endocrinological research on reproductive health following COVID-19. Data from the Michigan COVID-19 surveillance study showed that compared to the fully unvaccinated comparison group the prevalence of long covid was lower among vaccinated individuals [5].

The research question guiding our paper is how long-term COVID-19 affects female reproductive health, which stems from the recognition of a significant gap in our understanding of the effects of long-term COVID-19. While there has been considerable research about the acute effects of COVID-19 on the female reproductive system, especially its effects on menstrual health, there remains a gap in the literature investigating the long-term effects on broader aspects of female reproductive physiology and function. By combining the existing data and identifying gaps in our understanding, literature review such as this, plays a crucial role in advancing knowledge, guiding clinical practice, and educating the public on mitigating the long-term consequences.

Understanding the effects of long-term COVID-19 on the female reproductive system is crucial as it will foster important discussions and help develop interventions and therapeutic strategies to mitigate these effects. Furthermore, exploring the effects of long-term COVID-19 on the female rep system has a broader societal implication. By shedding light on the potential long-term consequences of covid 19 infection on fertility, pregnancy outcomes, and reproductive health broadly, we can empower individuals, healthcare professionals, and policymakers to make informed decisions regarding vaccination strategies. Reproductive planning and post-covid health care delivery. Fertility rates have decreased after the pandemic, according to data from high-income nations like the US, Canada, and Western Europe. This is probably because of shifting healthcare priorities, limited access to ART (Assisted Reproductive Technology), and economic uncertainty (Aassve et al., 2020). Conversely, lower-income nations, especially those in South Asia and sub-Saharan Africa, have demonstrated constant or rising fertility rates, which may be related to healthcare disruptions and limited access to contraception (Li et al., 2021).

These differences show that in order to lessen the long-term effects of COVID-19 on reproduction, region-specific healthcare treatments are required. Quantifying these changes and their effects on international reproductive health policy will require more study. This review aims to facilitate critical discussions, guide evidence-based care and management strategies, and ultimately improve outcomes for individuals affected by long-term COVID-19, particularly regarding reproductive health.



Methods

Different areas of the female reproductive system are affected by COVID-19, and the results vary as well. We reviewed the literature to determine the various effects of COVID-19. The 45 studies in this review covered a wide range of populations in high- and low-income settings and were located in North America, Europe, Asia, and Africa. Variations in menstrual health, fertility, pregnancy outcomes, and endocrine function were examined in studies including females of reproductive age who had previously contracted COVID-19.

Discussion

Long COVID and ovarian health affecting fertility.

COVID-19 has had significant lasting impacts on humanity and the propagation of humans. Despite the three significantly long and widespread outbreaks, rightfully the pandemic in 2020, 2021, and 2022 humankind continues to suffer at the hands of this virus. Long COVID is the condition defined in individuals having initial infections and extended symptoms up to 3 or more months [6]. The most commonly experienced symptoms by the patients are fatigue, cognitive dysfunction, post exertional malaise which are reported in all age groups.

The reproductive age group from 16-45 years has been the most vulnerable and affected class of the population by the COVID-19 pandemic. Apart from the multiple neurological, cardiovascular, and pulmonary complications; Long COVID has clawed around reproductive health and fertility too. Hereby focusing on female reproductive health, studies suggest that SARS-COV2 regulates the ACE2 receptor [7]. ACE2 receptor is present in all major organ systems like respiratory, cardiovascular, gastrointestinal, and renal and is highly expressed in the ovaries. Based on the studies, ACE2 plays a role in follicular development and ovulation, luteal angiogenesis,

and degeneration, affecting regular endometrial changes and fertility. Reis et al and colleagues confirmed the role of ACE2 markers and ACE2-MAS receptor axis in all stages of ovarian folliculogenesis being more prevalent in the epithelial cells - cuboidal epithelium than stromal cells. The expression of ACE2 is more abundant during the secretory phase - predominantly progesterone-producing than the proliferative phase(oestrogen-producing) of the cycle [8].

Long COVID has been evidenced more in women than men with specifically increased risk in premenopausal women. It's been known that ACE2 facilitates entry of SARS-COV2 into the target cells disrupting its function and regulation. Reproductive tissues also express TMPRSS2 and Basigin, two additional SARS-CoV-2 entrance routes in addition to ACE2. The viral spike protein is primed by TMPRSS2, which facilitates cell entry, and Basigin expressed in the uterus and ovaries, also allows entry of the virus into host cells, has been linked to interactions between ovarian and endometrial tissue [6]. Knowledge of these pathways adds to our understanding of COVID-19's possible long-term impacts on reproduction. The mechanism that drives the symptoms of long-term COVID-19 to persist are immune dysregulation and autoimmunity, pathogen persistence and reactivation, tissue and organ damage, and Microbiome dysfunction.

Reduced natural killer cell cytotoxic function, macrophage alterations, lowered cortisol, elevated oxidative stress, and allergies have also been evidenced to cause symptom extension of acute COVID-19 infection [6]. This leads to a long-term decline of ovarian health resulting in the risk of infertility in nulligravida or premature ovarian failure in gravid females.

Anti ovarian antibodies(AOA) are associated with autoimmune causes of premature ovarian failure. A case report from 2021 enlisted a female patient being treated for infertility who tested positive for AOA after contracting the COVID-19 infection [9]. Her hormone levels were monitored at each cycle and visit, but the finding for AOA was found positive specifically post- infection. To counteract the autoantibodies, a course of prednisone was given which helped to retrieve oocytes for IVF treatment. This suggests the possibility of transient oophoritis with COVID-19 infection.

COVID-19 has led to high levels of interleukin (IL)-6, IL-8, tumor necrosis factor-α, and other cytokines. The inflammatory mediator cascade leads to macrophage activation and cell damage in an attempt to eliminate the infection.

Ovarian reserve is a defining parameter for female fertility. It has been used to determine egg quality and quantity. Studies have shown that follicular fluid composition may be altered months after COVID-19 infection, which could affect oocyte quality and overall fertility. Levels of the cytokine IL-1 and vascular endothelial growth factors (VEGF) — key peptides in angiogenesis and vascular formation and thus, oocyte development — were lower in the follicular fluid of people undergoing assisted reproductive treatment 2 to 9 months (average 4.5 months, n = 46) post-COVID-19 compared to controls who were SARS-CoV-2-negative or never had COVID-19 symptoms (n = 34) [6].

Despite the pathological implications, the social impact of Covid 19 and female fertility has varied according to economic regions of the world [2]. Studies show that high-income countries recorded a decline in fertility during and after COVID-19 pertaining to the factors of reduced access to ART, economic losses, and increased uncertainty of circumstances. Middle and low- income countries depicted an equivocal rise in fertility due to reduced access to contraceptives and reduced development.

Thus, ovarian tissue and fertility were affected by Long COVID, and studies are underway that help to better understand the cause-effect relationship between these reproductive challenges.

Menstrual Cycle

The menstrual cycle in women varies in length (26-35 days), typically includes 5 days, and has a fertile phase extending from 5 days before ovulation to the day of ovulation, with fertility influenced by age and cycle length [10]. Menstrual bleeding patterns are considered relevant indicators of reproductive health, and changes in bleeding patterns may impact the quality of life for pre-and perimenopausal women. Irregular bleeding patterns and mid-cycle bleeding may be indicative of endocrine dysfunction and uterine abnormalities [11]. Emerging scientific evidence suggests that SARS-CoV-2 infection, and/or the psychological stress of the pandemic

may affect a woman's monthly cycle and female reproductive system [12, 13]. There is limited data about the impact of COVID-19 on the reproductive system, specifically the female reproductive system [13]. In one cross-sectional study (n = 1,792), over one-third of menstruating Long Covid patients reported an exacerbation of symptoms the week before or during menses [14, 16]. In another cross-sectional study (n = 460), 62% of LC patients experienced symptom worsening on days before menses [15, 16]. In a retrospective case-control study comparing the effects of vaccination (n = 4,989) and COVID-19 (n = 1,066) on menstrual health, it was discovered that a history of COVID-19, but not vaccination, was linked to a higher risk of missing periods, increased menstrual flow, menstrual cycle duration changes, and bleeding between periods [17, 18].

Recognizing the insufficient knowledge regarding the effects of the SARS-CoV-2 virus on the female reproductive system, the authors of this study endeavored to augment current understanding by incorporating data from women undergoing post-COVID-19 treatment. This methodology was employed to bridge gaps in knowledge concerning the impact of COVID-19 on the menstrual cycle in women [17].

Pregnancy

Numerous studies have been done to analyze the effect of long-covid on pregnancy, yet we are still unsure about the effects of long-covid on pregnancy. A cross-sectional study conducted in Ecuador compared the long-term effects of COVID-19 in pregnant (n=16) and non-pregnant women (n=231), revealing similarities in symptoms, particularly fatigue, hair loss, and difficulty concentrating. Similarly, a control-matched study in Brazil (n=88) followed pregnant women, diagnosed positive for covid (n=84), and found that 79% of these patients developed long-term symptoms of long-covid. Additionally, the patients who were administered glucocorticoids for the treatment of COVID-19 showed a higher incidence of fatigue. In the US, a cohort study done on pregnant women, showed 2% of pregnant women suffered from long-covid symptoms, persisting 8 weeks or more post-covid testing [19].

The biggest challenge faced by pregnant patients suffering from long-covid is the overlap of symptoms. Fatigue, shortness of breath, and cognitive impairment also known as brain fog are common in both pregnancy and long covid. Complicating matters further, symptom severity may fluctuate, with pregnant patients often reporting a worsening trend towards the third trimester [20].

Care for pregnant patients long-term is the same as any other patient with COVID-19. Including daily pulse monitoring, focus on sleep hygiene and balanced nutrition, abstaining from alcohol and smoking, and reducing caffeine intake. Addressing pre-existing conditions, administering antibiotics for secondary infections, and referral to specialists as needed e.g. mental health or pulmonary rehabilitation may be necessary. The patient should keep a symptom diary to aid in early diagnosis and management. Similarly, antenatal follow-up protocols remain the same as in any pregnant patient, with importance given to any deterioration of the existing symptoms or emergence of new ones [20].

Female Genital Tract

SARS-CoV-2 has been detected in various bodily fluids, but little is known about its presence in the female genital tract. [21] Limited studies have explored COVID-19's impact on this area.

There's a hypothesis that the virus could exploit ACE2 receptors in the endometrium and ovaries, potentially affecting follicular development and menstruation [22-24]. Because ACE2 is highly expressed in the human endometrium, SARS-CoV-2 might be able to infiltrate endometrial stromal cells and cause clinical symptoms in COVID-19-infected women. 1.If so, early pregnancy loss may be more likely to occur in women with COVID-19 [25]. Single-cell RNA sequencing analysis by Qi et al. identified the fallopian tube as particularly vulnerable to SARS-CoV-2 due to high ACE2 and TMPRSS2 expression, highlighting the importance of understanding viral susceptibility in the female reproductive system [26].

Aolymat, Iman et al observed increased incidences of abnormal vaginal discharge, itching, and lower abdominal pain in COVID-19 patients [27]. Xiao et al's meta-transcriptomic analysis revealed distinct differences in the vaginal microbiome of COVID-19 patients,

suggesting higher microbiota heterogeneity and more frequent detection of BV pathogens [28]. They suggested that immunosuppression or ICU antimicrobial treatments might contribute to these changes.

Activation of the NF-κB pathway, especially the IL-1/IL-36 pathway, was highlighted as critical in the female reproductive system's response to COVID-19 infection [27, 28].

Li et al.'s survey of 610 women of childbearing age revealed COVID-19-induced changes in the lower reproductive tract, such as altered vaginal discharge, vulvar pruritus, and vaginitis, particularly pronounced in those with prior pelvic inflammatory disease, ovarian cysts, or vaginitis. Longitudinal data suggest these effects are temporary and self-limiting, offering reassurance regarding COVID-19's impact on the reproductive system [29].

Studies done on small cohorts of pregnant, postpartum, postmenopausal, and women of reproductive age with SARS-CoV-2 show no virus in the vaginal fluid or cervical cells, suggesting no long-term effects in the lower genital tract [30-32]. Some reports suggest vaginal SARS-CoV-2 positivity, but the reasons for these discrepancies are unclear [33]. This is crucial for assessing vertical transmission risk in childbirth and guiding delivery methods for infected pregnant women.

Overall, the impact of SARS-CoV-2 on the female genital tract is not fully understood, with limited data available. While ACE2 receptor expression raises concerns, studies show mixed results, including abnormal symptoms and microbiome changes. However, some evidence suggests temporary effects, providing some reassurance. Further research is needed to understand long-term implications, especially regarding fertility and vertical transmission risk during childbirth, to inform clinical approaches for infected women.

The COVID-19 pandemic has precipitated a shift in the equilibrium of the female reproductive system toward oncopathology or chronic fibrosis.

The microbiome and viriome play crucial roles in tissue health, and emerging evidence suggests that COVID-19 can significantly impact these components. Severe cases of COVID-19 can reactivate oncogenic viruses like cytomegalovirus (CMV) and herpes simplex virus (HSV), potentially exacerbating tissue pathology [34]. Furthermore, COVID-19 may enhance SARS- CoV-2 entry into cells by activating ACE2, the virus's receptor, particularly in individuals with a history of human cytomegalovirus (HCMV) infection [35]. COVID-19 also triggers the expression of human endogenous retroviral elements (HERVs) linked to cancer development [36]. Notably, COVID-19 risk factors such as older age, obesity, and sex hormone levels overlap with risk factors for conditions like endometrial carcinoma (EC) and uterine fibroids (UF) [37-39]. Interestingly, while diabetes is a risk factor for COVID-19 and EC, it reduces UF risk [40]. Additionally, COVID-19 complications in pregnancy, such as gestational diabetes, highlight potential hormonal disruptions [41]. High levels of ACE2, the virus's receptor, in female reproductive tissues, emphasize the need to closely monitor potential pathological processes in these systems post-infection [42-47]. There is currently little data to support the increasing theories that extended COVID may be linked to fibrosis or oncopathology. Long-term SARS-CoV-2 infection-induced chronic inflammation has been linked in several studies to fibrotic tissue remodeling; nevertheless, further direct mechanistic research is required. It is important to interpret these relationships cautiously until stronger evidence is found.

Marker	*COVID-19*	*Fibrosis*	*Cancer*
ACE2	Soluble ACE2-creating complex increases at the onset of OVID-19 [48, 49]. In response to inflammation, it can be elevated [50]. Coronavirus infection could lead to a reduction in the presence of ACE2 receptors on the cell membrane. Decreased ACE2 levels are observed in diabetic individuals, and a history of diabetes is concurrently identified as a risk factor for COVID-19 [51].		ACE2 levels are elevated in endothelial cells compared to nearby noncancerous tissue [52].
Cathepsin B/L	Participate in the infection process of the target cell by SARS-CoV-2 [53].		
TMPRSS2	TMPRSS2 primes the SARS-CoV-2 S-protein at the cell membrane, preparing it for fusion with the host cell membrane [54].	Elevated in the human endometrium around the time of conception [55].	The level of expression is elevated in EC cells [56].
EMMPRIN (CD147)	A receptor responsible for cell entry [57].	The expression level is increased in individuals diagnosed with endometriosis [58], and it plays a role in fibrotic conditions such as uterine fibroids [59].	Prominent in EC [60].
Receptor tyrosine kinase (AXL)	Possibly implicated in SARS-Cov-2 entry into the host cell, independent of ACE2 [61].	Its expression is decreased in uterine fibroids compared to normal myometrial tissue [62].	Abundantly present in the endometrium and plays a role in the development of endometrial cancer [63].
Some human endogenous retroviral elements (HERVs)	Triggered [64].		Contribute in the formation of cancer characteristics [65]. The concentration of Syncytin-1 is notably higher in endometrial cancer (EC) [66]. Have significant functions in the onset and advancement of cancer [67].

Cytomegalovirus (CMV) and herpes simplex virus (HSV)	Undergo reactivation [68].		Might be involved in the development of endometrial cancer [69, 70].
IL-6, IL-1β, TNF-α, IFN-γ	COVID-19 leads to increased levels of these cytokines [71, 72]. Levels of IL-1β in the blood rise during the initial stage of SARS-CoV-2 infection and in individuals who have recovered from COVID-19 [73].		IL-6 and TNF-a have the potential to stimulate endometrial cancer (EC) [74, 75]. Levels of IL-6 and TNF-a are increased in tissue affected by endometrial cancer (EC) [76]. IL-6 also influences the expression of PD-L1 by EC Cells [77].
PD-1, PD-L1	In CD8+ T cells from individuals who have recovered from COVID-19, regulatory microRNA miR-15-5p, which targets PD1, was identified, indicating alterations in the PD- 1/ PD-L1 immune checkpoint pathway [78].		In endometrial cancer, the profiles of PD- L1 expression on tumour cells vary across molecular and histological subtypes [79]. Can be triggered by IFNγ [80].
Macrophages	Infection-induced hypoxia could potentially drive macrophage polarization within endometrial cancer (EC) more strongly toward the tumor- promoting phenotype [81].		The number of macrophages is higher in tumor tissue of endometrial cancer (EC) compared to the benign endometrium [82]. In hypoxic environments, endometrial cancer (EC) cells can induce monocytes to adopt a phenotype similar to M2 macrophages [83, 84].
ECM components	Have a substantial effect on the remodelling of the extracellular matrix (ECM) in lung tissue [85, 86].	Levels of Collagen 1A1, fibronectin, and versican are increased [87]. Functions in ECM- driven mechanotransduction, with ECM stiffness playing a pivotal role in the development of uterine fibrosis (UF) [88].	Aggrecan, nidogen, collagen type VIII chain α1, and collagen type XI chain α2 are increased in stage III endometrial cancer (EC) [89].
RAGE	SARS-CoV-2 can cause an increase in the activity of RAGE in various types of cells [90].		Levels are increased in endometrial cancer (EC) and primarily diminished in healthy tissue [91].

Mediator complex subunit 12 (MED12)	MED12 is associated with both DNA damage repair (DDR) and is identified within the SARS- CoV-2 protein interactome [92].	Mutations in the MED12 gene are frequently observed in uterine fibroids (UF) [93]. UF stem cells with mutations in MED12 exhibit increased levels of DNA damage [94].	
Chromatin	SARS-CoV-2 interferes with the regulation of chromatin in cells it infects [95].	It's marked by insufficient deposition of the H2A.Z histone [96].	Chromatin remodelling and DDR genes commonly undergo mutations as well [97].
Noncoding RNA		Crucial functions in the pathogenesis of uterine fibroids [98, 99].	Essential roles in the tumorigenesis of endometrial cancer [98, 99].

Table 1: Markers and its relation with Covid, fibrosis and Cancer.

Conclusion

In summary, this manuscript offers a detailed overview of the intricate relationship between long-term COVID-19 and the female reproductive system. It highlights how SARS-CoV-2 disrupts the renin-angiotensin system and interacts with ACE2 receptors in reproductive tissues, impacting ovarian function, menstrual patterns, and fertility. Moreover, it also discusses the role of immune dysregulation and autoimmunity in causing these disruptions. The discussion extends to the implications of COVID-19 on menstrual cycles, pregnancy outcomes, and female genital tract health, underscoring the necessity for interdisciplinary collaboration and diligent clinical monitoring. By advancing our understanding of these intricacies, healthcare providers can offer tailored care and interventions to mitigate the enduring effects of COVID-19 on women's reproductive health.

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