

Comparison of Prostate Health Index vs Prostate-Specific Antigen in Prostate Cancer Detection Among Men with Prostate-Specific Antigen 4 – 10 ng/ml

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Abstract

Original Research Article

Background: Prostate-specific antigen (PSA), although widely used for early detection, demonstrates limited specificity in the 4–10 ng/ml “gray zone,” frequently resulting in unnecessary prostate biopsies and associated morbidity. The Prostate Health Index (PHI), derived from [-2] proPSA, free PSA (fPSA), and total PSA (tPSA) using the formula $([-2] \text{ proPSA}/\text{fPSA}) \times \sqrt{\text{tPSA}}$, has been proposed to improve diagnostic discrimination in this subgroup. **Materials and Methods:** This one-year prospective comparative cross-sectional study was conducted at the Urology Division of Jos University Teaching Hospital. Men presenting with PSA levels between 4 – 10 ng/ml, regardless of symptoms or digital rectal examination (DRE) findings, were enrolled. Participants underwent clinical evaluation, DRE, measurement of [-2] proPSA, fPSA, and tPSA, and PHI calculation. All subjects subsequently underwent digitally guided transrectal prostate biopsy. Histologically confirmed adenocarcinoma was the primary outcome. Receiver Operating Characteristic (ROC) curve analysis was used to assess diagnostic performance. Statistical significance was set at $p < 0.05$. **Results:** Forty-two men (mean age 69.5 ± 9.5 years) were included. Prostate adenocarcinoma was detected in 5 patients (12%). Median PSA and PHI values were 7.0 ng/ml (IQR 5.0–9.5) and 12.1 (IQR 7.5–17.7), respectively. DRE findings showed a significant association with histological outcome ($p=0.000$). Although higher PSA and PHI values were observed in cancer cases, these associations were not statistically significant ($p=0.250$ and 0.405 , respectively). PHI demonstrated superior discriminative ability compared to PSA (AUC 0.668 vs. 0.538). A PHI cut-off value of 8.83 yielded 100% sensitivity and 35% specificity ($p=0.236$). **Conclusion:** PHI demonstrated improved diagnostic performance over PSA in men with intermediate PSA levels, although not statistically significant. PHI may serve as a useful adjunctive biomarker to reduce unnecessary prostate biopsies in this population.

Keywords: Prostate Health Index, Prostate-specific antigen, intermediate PSA, [-2]proPSA.

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INTRODUCTION

Prostate cancer (CaP) is the most diagnosed malignancy in men, typically affecting those in their seventh decade of life [1]. It is the second most prevalent and the fifth leading cause of cancer-related mortality in men worldwide [2]. Despite its significant global burden, mortality rates have declined in developed countries, likely due to early detection and advances in treatment.

The incidence of prostate cancer varies by race, with African American men having the highest risk compared to other racial groups [3]. In developed nations, standardized screening protocols and increased awareness have facilitated earlier diagnosis. Widely recognized screening tools for detecting CaP include

digital rectal examination (DRE) and prostate-specific antigen (PSA).

PSA remains the most widely used and effective single screening test for detecting prostate cancer and is often combined with DRE to improve its diagnostic yield [4]. However, while PSA is organ-specific, it is not disease-specific, limiting its ability to differentiate between benign prostatic conditions and prostate cancer. The lack of specificity of PSA in the 4 – 10 ng/ml range, the so-called diagnostic ‘gray zone’, where prostate cancer has been detected in 25% of men with palpably enlarged benign prostate gland, is particularly concerning [5]. A Nigerian study by Ezenwa *et al.*, [6]

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reported a 13.3% prevalence among patients with PSA within this range.

Several clinical parameters and PSA refinements have been developed to improve the specificity of PSA testing, particularly within the diagnostic gray zone in the early detection of prostate cancer. These derivatives include PSA density, PSA density of the transition zone, free PSA, % free PSA, age-specific PSA, PSA molecular forms, PSA velocity, % free/total PSA, % [-2] proPSA, etc [7-9]. Used individually or in combination, these parameters aim to reduce false-positive results and ultimately decrease unnecessary prostate biopsies, along with their attendant morbidities and costs [10].

One such important refinement is the Prostate Health Index (PHI), which is the focus of this research work. PHI is a mathematical formula that incorporates [-2] proPSA, free PSA, and total PSA (tPSA) and is expressed as $([-2] \text{ proPSA}/\text{free PSA}) \times \sqrt{t\text{PSA}}$. It is a multiplex test shown in several studies to be superior to its individual components in the detection of early prostate cancer, particularly in the PSA range of 4 – 10 ng/ml.

This study aimed to determine the usefulness of PHI in prostate cancer detection among Nigerian men with PSA levels of 4 – 10 ng/ml at the Jos University Teaching Hospital (JUTH), Nigeria. Since many men with PSA levels below 10 ng/ml have early-stage disease, improved detection can lead to timely treatment and reduce complications [11,12].

MATERIALS AND METHODS

1. Study Population

This hospital-based, comparative, prospective, single-center study was conducted from March 2022 to March 2023 in the Urology Division of JUTH, Jos. Sixty-two patients were enrolled after counseling and obtaining informed consent. The inclusion criteria comprised men presenting with complaints of lower urinary tract symptoms (LUTS) or asymptomatic men undergoing opportunistic screening with PSA levels of 4 – 10 ng/ml. Patients receiving 5- α reductase inhibitor treatment or those with urinary tract infection (UTI)/acute prostatitis or hematuria were excluded.

2. Study Procedure and Data Collection

Data for this study were collected using a structured proforma. After obtaining consent, each

participant underwent a detailed clinical evaluation, including relevant history, physical examination, and a DRE of the prostate. Blood samples were collected for total PSA, free PSA, and [-2]proPSA assays. Serum samples were separated into cryovials and stored at -20°C until analysis. The total PSA and free PSA were assayed using the Enzyme-Linked Immunosorbent Assay (ELISA) kits (Monobind Inc., CA, USA), while [-2]proPSA was assayed with a BT ELISA kit. Patients with total PSA outside the 4 – 10 ng/ml range after the analysis were excluded from the study: the standardization protocol. (Fig. 1). PHI was calculated as $([-2] \text{ proPSA}/\text{free PSA}) \times \sqrt{t\text{PSA}}$.

Transabdominal ultrasonography using a curvilinear probe of 3.5 Hz was performed by a radiologist to determine prostate volume. Eligible patients subsequently underwent digitally guided transrectal prostate biopsy.

The bio-demographics, clinical details like LUTS, DRE findings, serum [-2] proPSA, free PSA, total PSA, and histopathological report were analyzed.

3. Study Design

The study recruited 62 patients, of whom 20 were excluded due to PSA levels outside the gray zone. Consequently, 42 patients with PSA levels of 4 – 10 ng/ml were included as illustrated in the schematic study design (Fig. 1).

4. Statistical Analysis

Sociodemographic variables like age and educational status were summarized as frequencies and proportions, while quantitative variables were presented as mean \pm standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for the skewed data. Inferential analyses were performed using chi-square, t-test, and Fisher's exact test. The Receiver Operating Characteristic curve (ROC) was used to determine the diagnostic accuracy of PHI and PSA in prostate cancer detection. Statistical significance was set at p-value < 0.05.

RESULTS

The mean PSA in subjects with total PSA 4 – 10 ng/ml was 7.13 ± 2.2 ng/ml, and the median prostate volume was 60.7 ml (IQR: 38.7– 92.4 ml). The mean and median values of fPSA, [-2]proPSA, and PHI are shown in Table 1.

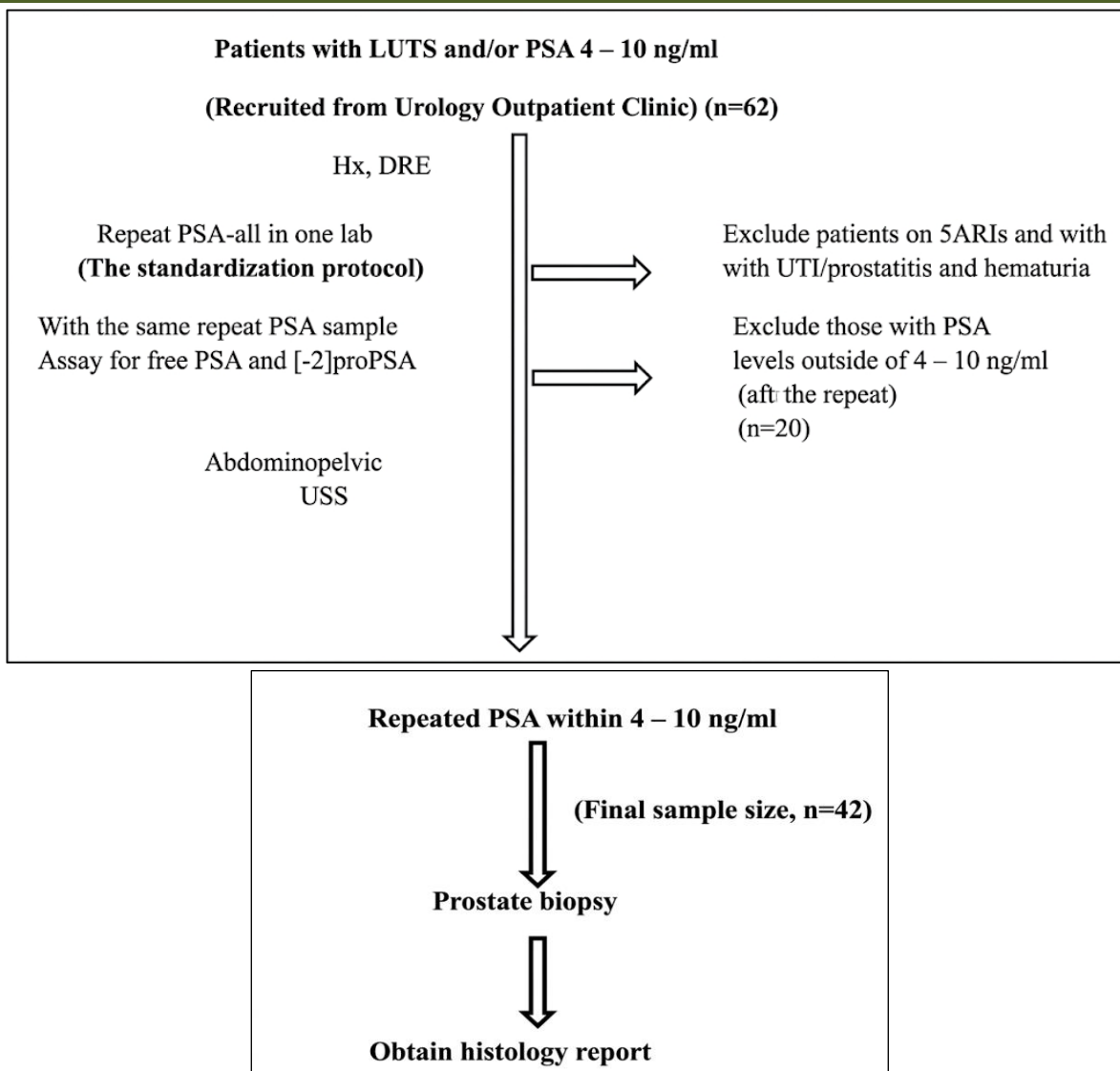


Figure 1: A flow chart showing the recruitment of patients
Hx- History taking, DRE- Digital rectal examination, 5ARIs- 5- Alpha receptor inhibitors, Laboratory, UTI- Urinary Tract Infection, USS- Ultrasound scan

Table 1: Mean and median of PSA variables and prostate volume in patients with LUTS and PSA 4–10 ng/mL (n=42)

Variable	Median (IQR)	Mean ± SD
Total PSA (ng/ml)	7.0 (5.0 – 9.5)	7.13 ± 2.2
Free PSA (ng/ml)	1.1 (0.8 – 1.7)	1.3 ± 0.7
[-2]proPSA (pg/ml)	4.9 (4.0 – 5.9)	5.3 ± 1.7
Prostate Health Index (PHI)	12.1 (7.5 – 17.7)	13.1 ± 7.3
Prostate Volume (ml)	60.7 (38.7 – 92.4)	72.6 ± 47.3

Prostate cancer was found more at higher values of PSA and PHI, as seen in Table 2; however, these findings were not statistically significant.

Table 2: Ranges of PSA and PHI values and percentage of adenocarcinoma in patients with LUTS and PSA 4 – 10 ng/ml (n=42)

Range of PSA	Percentage (%)	χ^2	p-value
4.0 – 6.0	14.3	2.770	0.250
6.1 – 8.0	0.0		
8.1 – 10.0	20.0		

Range of PHI			
0.0 – 9.9	6.3	1.807	0.405
10.0 – 19.9	11.1		
≥ 20.0	25.0		

The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of PSA in the range of 8.1 – 10.0 are 60.0%, 67.6%, 66.7%, 20.0%, and 92.6%, respectively.

The sensitivity, specificity, accuracy, PPV, and NPV of PHI in the range of ≥ 20 are 40.0%, 83.8%, and 78.6%, respectively. The sensitivities, specificities, and accuracies, PPV, and NPV at the different ranges of PHI are shown in Table 3.

Table 3: Sensitivity, Specificity, Accuracy, PPV, and NPV of PSA and PHI at different ranges in patients with LUTS and PSA 4 – 10 ng/ml (n=42)

Range of PSA	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
4.0 – 6.0	40.0	67.6	64.3	14.3	89.3
6.1 – 8.0	00.0	64.9	57.2	0.0	82.8
8.1 – 10.0	60.0	67.6	66.7	20.0	92.6
Range of PHI					
0.0 – 9.9	20.0	59.5	54.8	6.3	84.6
10.0 – 19.9	40.0	56.8	54.8	11.1	87.5
≥ 20.0	40.0	83.8	78.6	25.0	91.2

PPV- Positive Predictive Value, NPV- Negative Predictive Value

Receiver Operating Characteristic analyses on PSA and PHI were done to estimate their performances in the detection of prostate cancer in the PSA range of 4

– 10 ng/ml. PHI had a higher value of area under the curve (AUC) of 0.665, while PSA had a value of 0.538 (Fig. 2).

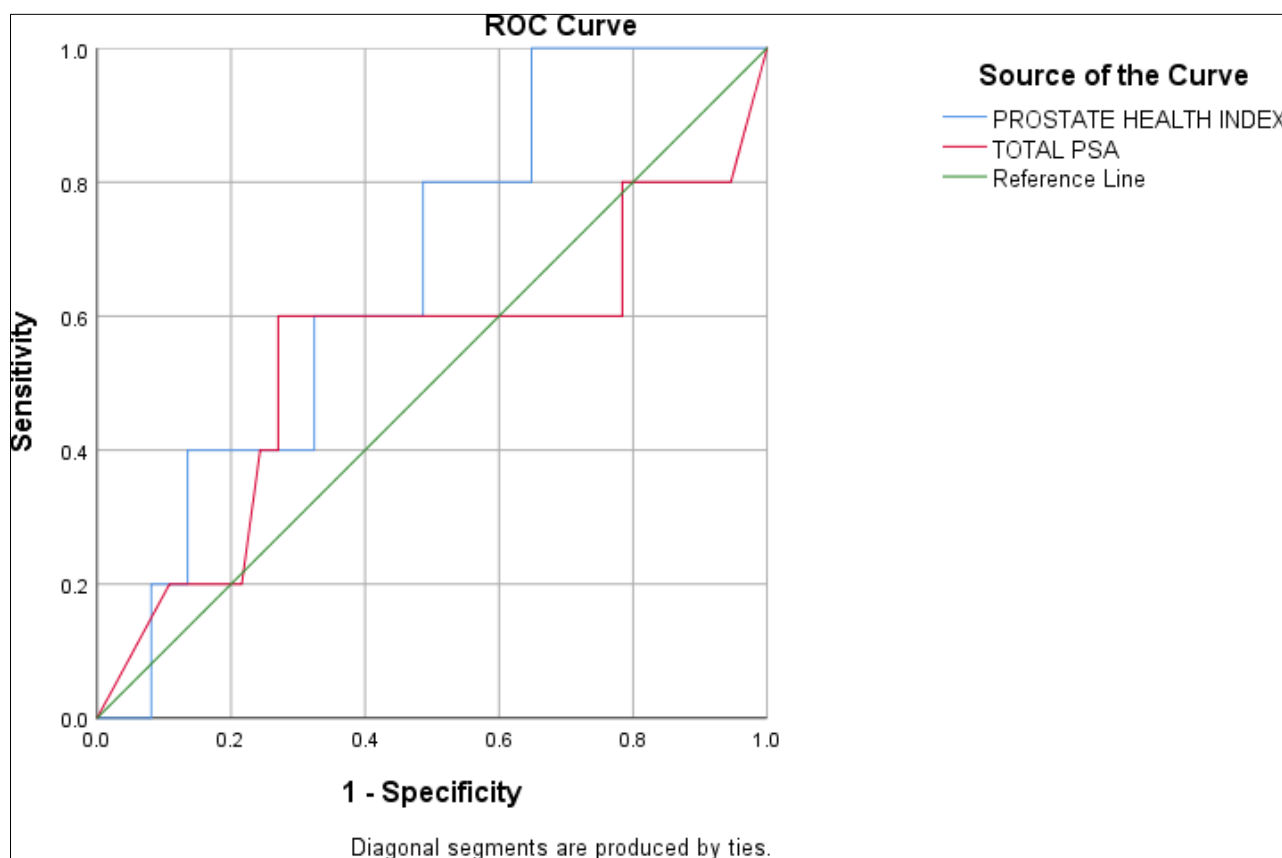


Figure 2: Receiver Operating Characteristic curves for PHI and tPSA scores in patients with LUTS and PSA 4 – 10 ng/ml (n=42)

PHI had an AUC of 0.665 compared to 0.538 for tPSA, although this was not statistically significant, as shown in Table 4.

Table 4: Comparison of Area Under the Curve for PHI and tPSA Scores in patients with LUTS and PSA 4 – 10 ng/ml (n=42)

95% CI					
Test Result Variable	Area	Std. Error	p-value	Lower Bound	Upper Bound
PHI	0.665	0.111	0.236	0.448	0.882
Total PSA (ng/ml)	0.538	0.164	0.786	0.217	0.859

The optimal cut-off value of PHI was estimated using Youden’s Index [Max (Sensitivity + Specificity - 1)]. The value was 8.83 with a sensitivity and specificity

of 100% and 35.1%, respectively; however, this was not statistically significant. This is shown in Table 5.

Table 5: Values for Area Under the Curve for predicting sensitivity and specificity of PHI at the optimal cut-off value of 8.83 in patients with LUTS and PSA 4 – 10 ng/ml (n=42)

Area	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value
0.665	8.83	100.0	35.1	17.2	100.0	42.9	0.236

PPV- Positive Predictive Value, NPV- Negative Predictive Value

DISCUSSION

This study evaluated the diagnostic accuracy of PHI compared with PSA for detecting prostate cancer in men with PSA levels of 4 – 10 ng/ml.

The observed prostate cancer prevalence was 12%, comparable to findings by Ezenwa *et al.*, (13.3%) [6] and another study conducted at JUTH (12%) [13]. The relatively lower prevalence rate in these studies, compared with reports by Catalona *et al.*, (25%) [5] and Tijani *et al.*, (22%) [14], may be attributable to the use of digitally guided transrectal prostate biopsy rather than TRUS-guided biopsy, which may improve cancer detection rates.

The median total PSA in this study was 7.0 ng/ml (IQR: 5.0 – 9.5). Most CaP cases occurred in the highest PSA range (8.1 – 10.0 ng/ml), with a prevalence of 20.0%, compared to 14.3% in the 4.0 – 6.0 ng/ml range and 0.0% in the 6.1 – 8.0 ng/ml range, indicating increased cancer occurrence at higher PSA values [15]. However, as noted by Yoshida *et al.*, PSA demonstrates low specificity within the diagnostic gray zone [16]. Consistent with prior studies, our findings showed low overall sensitivity (60.0%), specificity (67.6%), and positive predictive value (PPV) (20.0%) for PSA in the 8.1 – 10.0 ng/ml range [17-19].

This study analyzed PHI and found the median value of 12.1 (IQR: 7.5 – 17.7). The mean PHI was higher in patients with CaP (16.5 ± 6.7) compared to those with negative biopsy results (12.6 ± 7.4), indicating that increasing PHI levels are associated with a greater likelihood of cancer. This is consistent with the reports of other studies. [20-22] The PPV rose progressively across PHI ranges: 6.3% (0 – 9.9), 11.1% (10.0 – 19.9), and 25.5% (≥ 20.0). Similarly, Catalona *et al.*, reported increasing cancer detection rates with higher PHI ranges, further supporting PHI as a stronger predictive marker [20].

This study determined the PHI cut-off value of 8.83 for CaP detection, yielding a sensitivity of 100%, specificity of 35%, PPV of 17%, negative predictive value (NPV) of 100%, and accuracy of 43% (p=0.236). At PHI values above 8.83, the likelihood of adenocarcinoma of the prostate increases. The high sensitivity and NPV indicate that the threshold is effective in identifying patients with cancer and minimizing missed diagnoses. Various studies have proposed different PHI cut-off values depending on the study population. In predominantly White populations, higher thresholds have been reported, including cut-offs of 31.9 (specificity: 27.2%), [23] 48.5 (specificity: 42.9%), [24] and 22.8 (specificity: 25%) [25]. Similarly, Babajide *et al.*, [26], in an African American population, reported a cut-off of 28.0 with comparable specificity. These studies generally demonstrated higher PHI cut-off values than those observed in the present study. The discrepancy may be attributed to the racial differences, variation in sample size, and inclusion of PSA levels of 2 to 10 ng/ml in other studies.

Currently, no universally accepted PHI cut-off exists for CaP detection. Most proposed cut-offs aim to enhance specificity, thereby reducing false positive results and avoiding unnecessary prostate biopsies. However, increasing specificity often reduces sensitivity, potentially leading to missed cancer diagnoses, which carries a greater clinical risk. Therefore, there is a need to find a convenient trade-off between sensitivity and specificity, to avoid unnecessary prostate biopsies and limit the number of missed cancers. In this index study, a PHI cut-off (threshold) of 8.83 provided such a balance by maintaining maximal sensitivity while achieving moderate specificity, helping to reduce unnecessary biopsies without compromising cancer detection.

The area under the curve (AUC) was 0.665 for PHI and 0.538 for PSA, indicating better overall diagnostic performance of PHI, though this was not

statistically significant ($p=0.236$). A similar finding was reported where PHI was found to outperform PSA and even other PSA derivatives at various cut-off points. [21] Loeb *et al.*, [22] in a multicenter study of 658 men, reported that PHI provided better diagnostic accuracy than the other PSA variables and could potentially spare up to 30% of men in the PSA gray zone from unnecessary prostate biopsies. They concluded that PHI may be useful as part of a multivariable approach to reduce unnecessary prostate biopsies and overdiagnosis. Similarly, Bruzzese *et al.*, [27], in a meta-analysis, concluded that PHI used as a reflex test in men with gray-zone PSA levels improved the prediction of positive biopsy and reduced unnecessary procedures. However, not all studies uniformly support the superiority of PHI. Chiu *et al.*, [28] reported that PHI density (PHID) outperformed PHI in the detection of CaP in the gray zone (AUC: 0.82 vs 0.77). Other studies similarly suggest that alternative PSA-related variables or biomarkers may equal or exceed PHI performance in certain populations [29,30].

CONCLUSION

At a cut-off of 8.83, PHI outperformed PSA in detecting prostate cancer in the PSA range of 4 – 10 ng/ml. Although not statistically significant, PHI demonstrated 100% sensitivity and 35% specificity, potentially reducing unnecessary biopsies in over one-third of men while minimizing missed cancer cases compared to PSA alone.

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