Original Research Article

Estimated glomerular filtration rate and proteinuria – Predictors of left ventricular mass in chronic kidney disease

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Abstract

Background: Chronic kidney disease is a potential threat of the 21st century, afflicting more than 50 million people all over the world. Cardiovascular diseases particularly increased left ventricular mass accounts for 40 – 50% deaths of kidney disease patients.
Objective of the study: To find the factors which correlate with left ventricular hypertrophy in kidney disease patients.
Materials and methods: A descriptive study was done on 75 chronic renal failure patients for a period of 6 months. Variables like proteinuria, creatinine clearance, anemia, blood pressure, serum albumin and other blood parameters were compared with left ventricular mass.
Results: Of all the variables, the decline in estimated glomerular filtration rate and the increased amount of protein excretion affected the left ventricular mass index ($p < 0.01$). The mean GFR was 25 ml/min and the mean proteinuria > 3.5 g in females with left ventricular hypertrophy (>110 g/m^2). With the cut-off for left ventricular hypertrophy in male > 134 g/m^2, the mean GFR was 20 ml/min and the mean proteinuria more than 7 g/L.
Conclusion: Measures to decrease the amount of proteinuria and the rate of decline in glomerular filtration rate will prevent significant cardiovascular disease in chronic kidney disease patients.

Key words

Chronic kidney disease, Cardiovascular disease, Estimated glomerular filtration rate, Proteinuria, Left ventricular mass, Devereux formula.

Introduction

Chronic Kidney Disease is the burgeoning health epidemic of the 21st century. This disease is a potential threat with an increasing incidence and prevalence, poor outcomes and high cost [1]. More the 50 million people all over the world are afflicted by kidney disease. Over 2 million people require renal replacement therapy to sustain life worldwide, which represents less than 10% of the needy population [2]. Looking into the risk factors, diabetes and hypertension top the rank list worldwide. With the rising burden of diabetes and hypertension, chronic kidney disease is becoming a major public health problem. According to the World Health Statistics of 2013, one in three adults has hypertension and one in ten adults have diabetes worldwide [3]. Apart from the major risk factors mentioned, poverty and social deprivation are emerging as major risk factors for chronic kidney disease in both developed and developing countries.

Outcomes of chronic kidney disease include not only kidney failure but also complications of decreased kidney function and cardiovascular disease. About 40 – 50% of the death in chronic kidney disease is attributed to cardiovascular causes [4]. In particular increased left ventricular wall thickness is found to underlie this predisposition [5]. Individuals with the most severe form of chronic kidney disease have a risk for cardiac death that is 14 times higher than similar patients who differ only in that their glomerular filtration rate is greater than 60 ml/ minute. Current evidence suggests that some of these adverse outcomes can be prevented or delayed by early detection and treatment [6]. If the risk factors which contributed to increased left ventricular thickness in chronic kidney disease patients could be lined out, it would be easier to treat them [7].

So, we conducted a prospective descriptive study in 75 CKD (chronic kidney disease) patients attending our nephrology department to check for the variables of kidney disease that correlated with increased left ventricular mass. This study uses the variables- 24 hour proteinuria, estimated glomerular filtration rate, serum albumin, hemoglobin, serum phosphorus, total cholesterol and triglyceride levels to predict the left ventricular mass in chronic disease patients.

Objectives of the study

- To calculate the left ventricular mass of chronic kidney disease patients who are on conservative medical management.
- To calculate the glomerular filtration rate of CKD patients using 24 hour creatinine clearance and Cockcroft Gault formula. To calculate the amount of proteinuria in CKD patients using urine spot PCR [protein creatinine ratio] and 24 hour quantification.
- To study whether there is a relationship between the amount of proteinuria and the glomerular filtration rate to the left ventricular mass.

Materials and methods

Study design and data collection

A descriptive case study was done on 75 chronic kidney patients admitted in the Nephrology ward and attending the Nephrology Outpatient Department of Dhanalakshmi Srinivasan Medical College Hospital over a period of 6 months from April 2018 to October 2018. CKD patients less than 18 years, with history of cigarette and alcohol consumption, obesity, athletic training, on maintenance hemodialysis treatment, with arterio-venous fistula or post renal transplant status, with aortic stenosis or insufficiency, hypertrophic obstructive cardiomyopathy were excluded from the study.

A Data collection form was prepared to note the Age, Sex, Occupation, Address, Complaints, Past Medical History, Smoking, Alcoholism, Drug Intake and other relevant history. General Examination with examination of the Vital Signs, Cardiac, Respiratory, Abdomen and Central Nervous System were done. Blood samples and urine samples were drawn at the time of admission and in the Outpatient department for urine spot protein creatinine ratio calculation and renal function test. 24 hour urine collection was scrutinized and analyzed for proteinuria quantification and creatinine clearance. Left ventricular mass is measured using 2D Echocardiography. Devereux formula was used for the calculation of left ventricular mass index [8].

Calculations and definitions:

Urine creatinine value:

Urine creatinine (24-hour sample) values can range from 500 to 2000 mg/day. Results depend greatly on age and amount of lean body mass

Creatinine clearance formula:

[Urine creatinine (mg/dL)] × [24-Hour Urine Volume (mL/day)/1440 (min/day)]
[Serum Creatinine (mg/dL)]

Cockcroft Gault formula:

(140 – Age) × Mass (in kilograms) × [0.85 if female]
72 × Serum Creatinine (in mg/dL)

Modified Devereux formula:

Left ventricular mass is calculated using the American society of echocardiography formula modified by Devereux

LV mass: 0.8 (1.04 ([LVIDD + PWTD + IVSTD]^3- [LVIDD]^3))+ 0.6

LVIDD = Left Ventricular Internal Diameter in Diastole
PWTD = Posterior Wall Thickness in Diastole
IVSTD = Interventricular Septum Thickness in Diastole

Left ventricular mass index

Left ventricular mass (g)
Body surface area (m^2)

Left ventricular hypertrophy was defined in absolute terms as LVMI >134 g/m^2 in men and >110 g/m2 in women

Statistical methods

Data were entered in Microsoft Excel Spreadsheet and analyzed using SPSS software. Categorical variables were expressed in frequency and percentages. Continuous variables were expressed in mean and standard deviation. Student 't' test was applied as the test of significance. 'p' value less than 0.05 was considered statistically significant.

Results

Study population characteristics

A total of 75 CKD patients between ages 18 to 60 years were included in this study, of which 35 were females and 40 were males. Patients in this study were divided into two group based on their LVMI (left ventricular mass index). About 61% of our study patients had increased left ventricular mass on Echocardiography. Female with LV mass index more than 110 g/m^2 and male with LV mass index more than 134 g/m^2 were categorized as abnormal/ increased left ventricular mass group and those patients with values below than this are categorized as the group with normal left ventricular mass. Baseline characteristics of the study population were as per **Table – 1**. Clinical data of the normal and abnormal LV mass group was as per **Table – 2**.

The percentage of males with normal LVMI was 37.5% and abnormal LVMI was 62.5%. Similarly, the percentage of females with normal LVMI was 40% and with abnormal LVMI was 60%. The "p" value between the two groups male and female with regard to the variable left ventricular mass index was 0.824. Hence the sex difference regarding the left ventricular wall thickness was not significant.

Table - 1: Baseline characteristics of the study population.

VARIABLE		NORMAL LVMI	ABNORMAL LVMI	TOTAL	p VALUE
Gender	Male	15 (37.5%)	25 (62.5%)	40	0.824
	Female	14 (40%)	21 (60%)	35	
Diabetes	Yes	15 (42.9%)	20 (57.1%)	35	0.486
	NO	20 (57.1%)	15 (42.9%)		
Systemic hypertension	Yes	15 (37.5%)	25 (62.5%)	40	0.824
	NO	25 (62.5%)	15 (37.5%)		

* Correlation was significant at the 0.05 level (2-tailed).

Table - 2: Clinical data of the normal and abnormal LV mass group.

Variable	LVMI	N	MEAN	STANDARD DEVIATION	p VALUE
Age	Normal	29	41.21	9.507	0.912
	Abnormal	46	40.89	10.963	
Duration of CKD	Normal	29	3.52	1.184	0.28
	Abnormal	46	3.7	1.685	
Systolic blood pressure	Normal	29	124.55	12.07	0.65
	Abnormal	46	122.87	13.055	
Diastolic blood pressure	Normal	29	81.93	5.669	0.131
	Abnormal	46	79.87	4.87	
Serum albumin	Normal	29	2.934	0.3866	0.12
	Abnormal	46	2.781	0.3308	
Hemoglobin	Normal	29	8.33	1.052	0.406
	Abnormal	46	8.44	1.042	
Serum alkaline phosphatase	Normal	29	285.86	77.969	0.451
	Abnormal	46	290.65	64.339	
Serum cholesterol	Normal	29	206.07	67.928	0.667
	Abnormal	46	198.52	64.181	
Serum triglycerides	Normal	29	166.24	51.465	0.895
	Abnormal	46	167.07	55.569	
Blood urea	Normal	29	76.97	48.252	0.41
	Abnormal	46	93.67	36.531	
Serum creatinine	Normal	29	1.872	0.7745	<0.001*
	Abnormal	46	6.515	2.6802	
Waist/ hip circumference	Normal	29	0.8010	0.06863	0.011
	Abnormal	46	0.7691	0.07158	
Body surface area	Normal	29	1.5962	0.16146	0.713
	Abnormal	46	1.5996	0.18959	

* Correlation was significant at the 0.05 level (2-tailed).

The two risk factors commonly associated with chronic renal failure are diabetes and systemic hypertension. The number of diabetics in the study group was 35 and the distribution between the normal LVMI group (43%) and abnormal LVMI group (57%) was not statistically significant (p=0.486). The number of hypertensive patients in the study group was 40 and the distribution between the normal LVMI group (37.5%) and the abnormal LVMI group (62.5%) was not statistically significant (p=0.824).

Regarding the age of the study group, people in all age group were evenly distributed in the study population. The mean age in the normal left ventricular mass group was 41 and in the abnormal left ventricular mass group was 40, there was no clinical nor statistical difference (p=0.13) between the two groups.

Chart - 1: Comparison of serum creatinine value with LVMI.

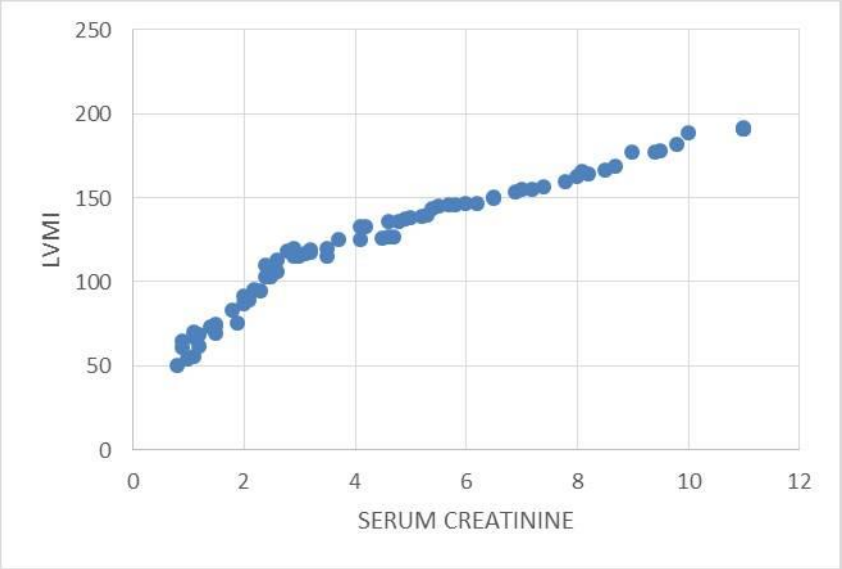
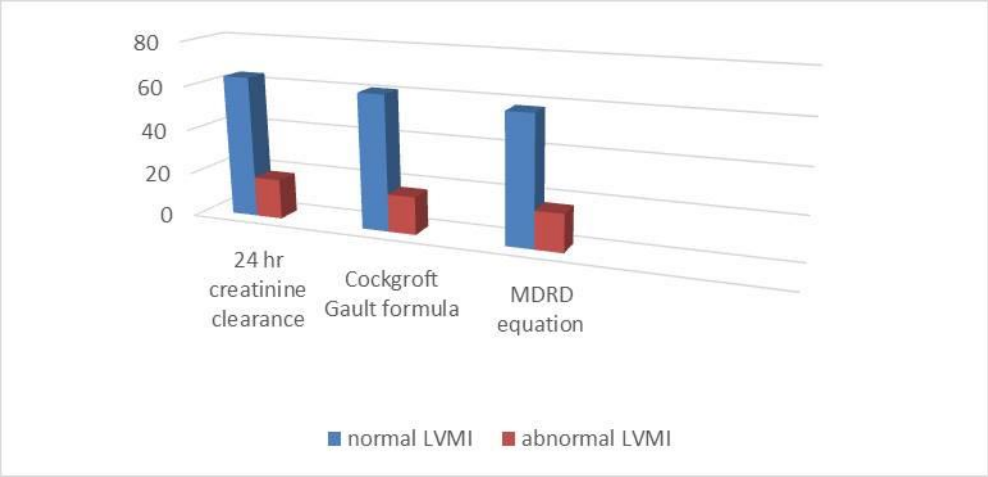


Table - 3: Clinical data of the normal and abnormal LV mass group.

VARIABLE	LVMI	N	MEAN	STANDARD DEVIATION	p VALUE
24 hr creatinine clearance	Normal	29	64.28	20.898	<0.001*
	Abnormal	46	17.96	9.328	
Creatinine clearance (CCG)	Normal	29	61.17	15.531	<0.001*
	Abnormal	46	17.39	9.332	
Creatinine clearance (MDRD)	Normal	29	58.69	14.912	<0.001*
	Abnormal	46	17.09	9.904	
Urine spot PCR	Normal	29	1.8224	0.96362	<0.001*
	Abnormal	46	10.8097	6.01479	
24 hr proteinuria	Normal	29	1821.62	969.84	<0.001*
	Abnormal	46	8621.74	3457.595	

Chart - 2: Comparison of eGFR obtained by various methods with LVMI.



In our study group, more number of patients were having CKD of the duration of 2 to 5 years. On comparing the duration of chronic kidney disease with the left ventricular mass index, there was no clinical (normal LVMI mean duration 3.5 years vs. abnormal LVMI mean duration 3.7

years) nor statistical difference (p=0.254) between the two study groups.

In this descriptive study, the association between variables like systolic and diastolic blood pressure, serum albumin, hemoglobin, serum alkaline phosphatase, serum cholesterol and triglycerides, blood urea and creatinine, proteinuria (urine spot PCR, 24 hour quantification) and glomerular filtration rate (using the formulas 24 hour creatinine clearance, Cockcroft Gault and MDRD equation) were studied as an independent risk factor for the left ventricular hypertrophy of CKD patients.

The average systolic blood pressure in the normal LVMI group was 124 mmHg and in the abnormal LVMI group was 123 mmHg, so there was no clinical nor statistical significance (p=-0.53). Similarly there was no statistical significance regarding the variable diastolic blood pressure (p=-0.176) between the normal LVMI group (82 mmHg) and the abnormal LVMI group (80 mmHg).

The average hemoglobin in the normal LVMI group was 8.3 g/dL and in the abnormal LVMI group was 8.44 g/dL implying that there was no significance (p=0.097) between the groups regarding the variable hemoglobin.

With regard to the liver function test, the serum albumin in the normal LVMI group was 2.9 g/dL and in the abnormal LVMI group was 2.78. There was no statistical significance (p=-0.181) between them. The serum alkaline phosphatase levels were not statistically significant (p=0.088) between the normal LVMI group (285 U) and the abnormal LVMI group (290 U).

On comparing the lipid profile between the two groups, there are no clinical or statistical significance between them regarding the variables serum cholesterol (p=0.05) and triglycerides (p=-0.015). The mean serum cholesterol value in the normal LVMI group is 206 mg/dL and in the abnormal LVMI group was 198 mg/dL. The mean serum triglycerides level in the normal group was 166 mg/dL and in the abnormal group 167 mg/dL.

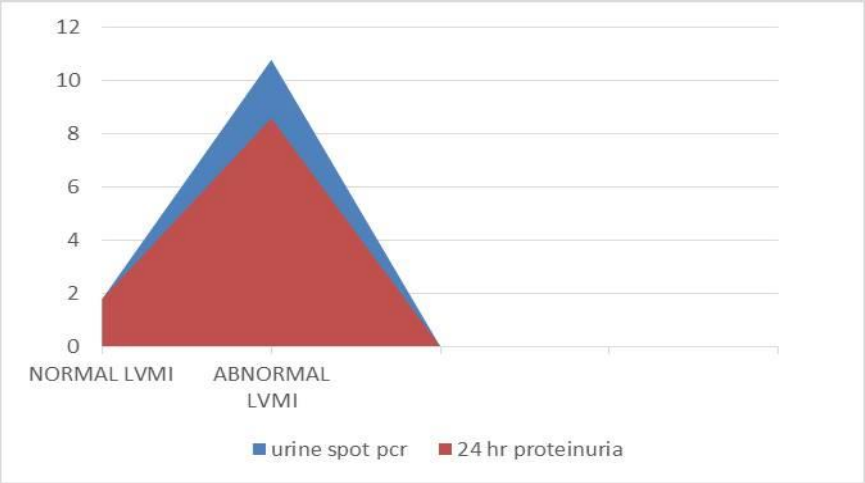
There was no statistical significance between the variables waist/ hip circumference and body surface area when compared with the left ventricular mass index. The average WHR in the normal LVMI group was 0.8 and in the abnormal LVMI group was 0.7 with no statistical significance (p=-.293). The average BSA in the normal group was 1.59 and in the abnormal LVMI group was 1.59 with no statistical significance (p=-.043).

The average serum creatinine value in the normal LVMI group was 1.8 mg/dL and in the abnormal LVMI group was 6.5 mg/dL implying that as the stage of CKD progresses, there was a definite risk of cardiovascular disease as left ventricular mass increases. There was clinical and statistical significance (p<0.001) between the two groups. Comparison of serum creatinine value with LVMI was as per **Chart – 1**. The prevalence of left ventricular hypertrophy tends to increase with progression of renal decline (22.7% in stage 3 CKD, 43.6% in stage 4 and 48.3% in stage 5 CKD). Clinical data of the normal and abnormal LV mass group was as per **Table – 3**.

The glomerular filtration rate in the study population ranged from near normal to severe oliguria and end stage renal disease. On calculating the GFR value using the formulas 24 hour creatinine clearance, Cockcroft Gault and MDRD equation, it was statistically significant (p<0.001) when compared to the left ventricular mass. The GFR value according to 24 hour creatinine clearance in the normal group was 64 ml/min and in the abnormal LVMI group was 18ml/min. On using the Cockcroft Gault formula for eGFR, the average value in the normal LVMI group was 61 ml/min and in the abnormal LVMI group was 17.3 ml/min. The MDRD equation gave an eGFR value of 58 ml/min in the normal group and 17 ml/min in the abnormal LVMI group. Comparison of eGFR obtained by various methods with LVMI was as per **Chart – 2**.

All the patients in the study have proteinuria ranging from physiological limits to nephrotic range and massive protein excretion. The urine spot PCR in the normal LVMI group was 1.8 g/g/dL and in the abnormal LVMI group was 10.8 g/g/dL. The 24 hour proteinuria value for the normal LVMI group was 1.8 g/L and for the abnormal LVMI group was 8.6 g/L. When comparing the protein excretion of CKD patients to left ventricular mass index, it was clinically and statistically significant ($p<0.001$). Comparison of proteinuria (urine spot PCR and 24 hour proteinuria) with LVMI was as per **Chart – 3**.

Chart - 3: Comparison of proteinuria (urine spot PCR and 24 hour proteinuria) with LVMI.



Discussion

In our study, we included 75 cases of known chronic kidney disease on conservative management. Patients with uncontrolled hypertension, on maintenance hemodialysis, on arteriovenous fistula and other factors which influenced the left ventricular mass independently are excluded from the study.

In an article by Kimura, et al. [9], a Japanese journal, Left ventricular hypertrophy which is a strong predictor of mortality in chronic kidney disease patients is present in over 70% of patients commencing dialysis. The prevalence of left ventricular hypertrophy tends to increase with progression of renal decline (22.7% in stage 3 CKD, 43.6% in stage 4 and 48.3% in stage 5 CKD). In our study 61% of the patients have increased left ventricular mass on Echocardiography and the prevalence of left ventricular hypertrophy is 21.7% in stage 3 CKD, 35.6% in stage 4 and 45.6% in stage 5 CKD.

In an article by Daniel E Jesuorobo [10], Port-Harcourt Teaching Hospital, Nigeria, mean arterial pressure and eGFR were identified as predictors of LVH among CKD patients. In a study by Yilmaz BA, et al. [11], Ankara University, Turkey, systolic blood pressure, age, inflammatory markers like C - reactive protein and decrease in glomerular filtration rate was found to be an independent predictor of left ventricular thickness in chronic kidney disease.

In our study, we found a statistically significant correlation of declining GFR (Stage 4/5) [the mean GFR is 25 ml/min for females and the mean GFR 20 ml/min for males] with increased left ventricular thickness. The other variable which correlated with increased left ventricular mass is the serum creatinine level. Since the serum creatinine levels are a direct marker of the kidney function, thereby the glomerular filtration rate, it is obvious that eGFR is an independent predictor of LV mass in our study.

Moving to the association between proteinuria and left ventricular hypertrophy, in a study by Emily P McGuarrie [12], Glasgow University, an independent and significant association between

the level of urinary protein excretion and left ventricular mass was seen. This relationship was independent of the baseline systolic blood pressure. In our study, the mean proteinuria is more than 3.5 g in females and more than 7 g in males in the increased LVMI group implying that proteinuria is an independent predictor of left ventricular mass in kidney disease patients.

In this study, we also analyzed the association of other variables in CKD like serum albumin, age, gender, body mass index, hemoglobin, serum albumin, serum alkaline phosphatase, blood urea, waist hip ratio, body surface area, total cholesterol and triglyceride levels with increased left ventricular mass. We did not find any significant association between the above said variables and left ventricular hypertrophy in our patients.

Recommendations

To prevent cardiovascular morbidity and mortality in kidney disease patients, the following guidelines are advised:

- Meticulous control of 24 hour blood pressure (target of 130–140 mmHg systolic) and proteinuria [13]. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers may be preferred.
- Rigorous control of extracellular and intravascular volume should be the highest priority (NaCl restriction, inter dialysis fluid restriction, suppression of inter dialysis weight gain, loop-acting diuretics, ultrafiltration). Utilization of more frequent and/or longer dialysis (nocturnal haemodialysis, daily in-centre haemodialysis) is strongly encouraged [14].
- Treatment of disorders of divalent ion metabolism (maintain serum phosphorus at 4.0–6.0 mg/dl) is desirable. Treat severe hyperparathyroidism (maintain parathormone- 500 pg/ml) in ESRD. Avoid vitamin D deficiency (keep serum levels of 25OH cholecalciferol - 30 ng/ml)
- Avoid high-dose EPO (erythropoietin); maintain haemoglobin 10 - 12 g/dl. Maintain adequate iron stores with regular use of parental iron, in small individual doses.
- Consider prophylactic use of cardio-selective Beta blockers (e.g. Carvedilol) in subjects at high risk. Prescribe beta blockers routinely if a prior coronary artery disease–related event has been documented [15].

Monitor the course of LV mass after dialysis every 12–18 month (by 2-D ECHO, 3-D ECHO, or CMRI without gadolinium contrast in treated ESRD; dialysis).

Limitations

The prediction that eGFR and proteinuria is directly proportional to the left ventricular mass in our study could not be confirmed and generalized due to limited sample size.

The other variables which cause left ventricular hypertrophy in chronic kidney patients like anaemia, volume overload, increased systolic and diastolic blood pressure could not be completely confounded in the study group.

The effect of haemodialysis and adequate hemofiltration on the left ventricular mass of chronic kidney patients is not included in the study.

Conclusion

The global economic impact of chronic kidney disease is tremendous. Cardiovascular events are the most common cause of morbidity and mortality, accounting for 40 – 50% of CKD patients. In this study, on analysing the risk factors which contributes to increased left ventricular wall thickness, the rate of decline in estimated glomerular filtration rate and the amount of proteinuria are statistically significant to left ventricular mass index. Hence, the early prevention of massive proteinuria and

progressive decline in the glomerular filtration rate with drugs and dialysis could improve the cardiovascular health of CKD patients. Therefore, it's high time now to take a step to break this vicious cycle of coronary events and sustain the struggle of patients to lead a normal life.

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