Interleukin-10 gene polymorphism in COVID-19 patients and outcome of disease

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Abstract
More than 2 years into the COVID-19 pandemic with more than 6 million death worldwide , a dysregulated immune response to the pathogen associated with super-activation of pro-inflammatory cytokines, which may cause tissue injury, particularly lung tissue , IL -10 levels can impact on the clinical performance of the patients . this search conducted to detect the effect of Interleukin-10 gene polymorphisms on severity and outcome COVID-19 patients. A case – control study design for 120 COVID-19 patients that divided into sever, critical and moderate/mild patients in addition to 60 healthy subjects as control group to compare IL-10 serum level by ELISA technique and IL-10 gene polymorphism by ARMS-PCR assay. The result illustrated that 120 patients with covid-19 disease m classified as Critical cases 33 (27.5%), sever 42 (35%) and Mild/Moderate were 45 (37.5%). IL-10 increased in the serum of Covid-19 pneumonia patient's to (48.76 ± 12.3) pg / ml in compared with healthy controls (5.47±1.33) pg/ml. genotype results revealed that IL-10 gene distribution was GG homozygous (58.3%) higher in Covid-19 patients in compared to healthy controls (21.7)% and G allele was 124 for patient and 42 for healthy , so GG consider risk factor for coronavirus while AA genotype regard protective factor with frequency reach to 12% in patients and 48.3 % in healthy. The genotype distribution for critical/sever revealed the GG was 74.7% while in M/M was 31.1%. In conclusion: a significant association of GG genotype and allele G was observed with severity of COVID-19 infection.
Keywords: IL-10 gene polymorphisms, severity, COVID-19

1. Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus the midst of worldwide panic and global health concern expanded dramatically throughout the world and became an important global crisis and battle against this deadly virus , respiratory symptoms ranging from critical ,severe, moderate to mild stats , some of those who become infected develop severe symptoms and require medical attention (Carman *et al.*, 2022)
The host genetic polymorphisms play a key role in the susceptibility or resistance to different viral infections (Ramos-Lopez *et al.*,2020). It seems that a combination of multiple genes might be involved in COVID-19 pathogenesis . Accordingly, some studies have indicated that polymorphisms in genes related to innate and adaptive immune response and cytokines/chemokines are associated with COVID-19 development and/or severity (SeyedAlinaghi *et al.*,2021 ; Dieter *et al.*,2022).
IL-10 is a class-II cytokine mostly produced by T helper-2 cells, regulatory T cell , NK-cells has anti-inflammatory activity through the blocking of pro-inflammatory cytokines production and reducing the expression of MHCII molecules (Asgharzade *et al.*,2022)
Interleukin- 10 gene (−1082 G/A) polymorphisms in the promoter region linked to different expression levels of this cytokine , IL10 haplotypes are associated with many aspects of different diseases and conditions, including survival and relapse in critical HBV, systemic lupus erythematosus and asthma (Surhan et al.,(2018) ; Hatem and Darweesh (2019) . Elucidating the genetic determinants of SARS-CoV-2 infection is essential for understanding the pathophysiology of COVID-19 . So this search aimed to detect the impact of Interleukin-10 gene Polymorphisms and serum level on severity and outcome COVID-19 patients in AL-Najaf provinace /Iraq

2. Patients and Method

A Case - control study was design, during june-October2021 for 120 patients attended Al-Najaf AL-Ashraf National center for COVID-19 screening whom diagnosed by physicians , in addition to 60 healthy subjects as control group . Three milliliters of venous blood samples were taken from all subjects: 1 ml was put in a gel tube to separate serum in centrifuged (at 3000 r.p.m for 5 minutes) and kept at (-20) °C used to evaluate the level of IL-10 according to (Solarbio \ China) by ELISA technique (Biotech\USA). and the second portion (2 ml) was transferred into the anticoagulant tube for extracted DNA by (favorgen kite/ china) to detected IL-10 gene polymorphism by ARMS-PCR assay.
Genomic DNA was extracted from fresh peripheral blood (2 ml in EDTA) using a commercially available kit according to the protocol of favorgen/china and stored at -20 C till use. Single nucleotide polymorphisms (SNPs) related to the IL-10 (-1082) were determined using PCR with Amplification Refractory Mutation- Polymerase Chain Reaction (ARMS-PCR) in two reactions employing one

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common forward and two reverse primers 5′-AGCAACACTCCTCGTCGCAAC-3′ (forward) ,5′-CCTATCCCTACTTCCCCC-3 (reverseone) and 5′-CCTATCCCTACTTCCCCT3′ (reverse two) with an amplicon size of 179 bp. The reaction mix was done in 25µl volumes include 5µl of template DNA, GoTaq ®Promega Green Master Mix 2X 12.5 µl, Primers (foreword 2 µl and reverse 2 µl) and Nuclease Free water 3.5 µl (Applied PCR system, USA).and PCR conditions for *IL0* gene are initial denaturation at 94°C for 5 min, followed by denaturation at 94°C for 30s,annealing at 60°C for 1 min and 1 min of extension at 72°C, with a final extension of 7 min at 72°C .The resultant PCR products were resolved by electrophoresis(UV - Trans illuminator) on 1g agarose gel stained with 2 µl (0.5 % concentration) from ethidium bromide, the run lasted for 1 hour for 80 V. The gel was then photographed by digital camera on UV light and scored for the presence or absence of an allele specific band.

Inclusion and Exclusion Criteria

Patients suffering from COVID-19 were included while patients with chronic disease , other type of respiratory diseases , bacterial pneumonia were excluded.

Ethical considerations

The study concept was accepted by Institutional Ethics Committee for Human Studies from Al-Najaf AL-Ashraf National center for COVID-19 screening and the College of Science at Kufa University. In addition, all of the subjects provided written informed consent prior to participating in the research.

Statistics

Analysis of data was performed by using Statistical Package for Social Science (SPSS) system/ version 20. Results of ELISA expressed as mean ±S.E. Differences of genotype and allele frequencies between Covid-19 and control groups were also analyzed using the 2 test, 95% condense intervals (CIs) and odds ratios (ORs) for the risk of infection using logistic regression analysis. The difference was considered significant $p < 0.05$.

3. Result and Discussion

Demographic characteristics for 120 patients with Covid-19 disease which divided into Critical 33 (27.5%) , sever 42 (35%) and Mild/Moderate 45 (37.5%), In addition to (60) apparently healthy subjects as control group. Male recorded 68 (56%) in patients and the controls recorded 32 (53.3%) for male, the results revealed non-significant differences (P=0.926) in number and percentage of Covid-19 patients and healthy according to gender groups. The results appear that median age of patients were 63 (14-72) with high frequency in patients between age 46-60 were 32.5 years, there is no-significant difference with control group who found that median age 60 range (15-69) with high frequency in age between (46-60) were 36.6 years.

Table (1). Demographic distribution for Covid-19 patients and healthy

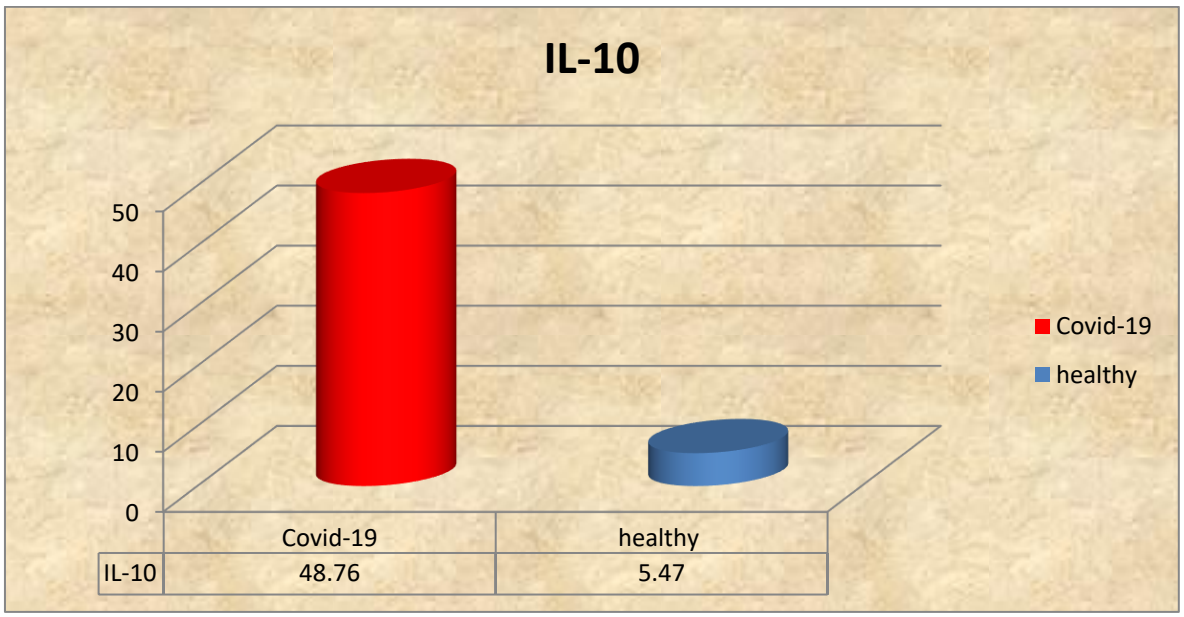
parameter	Covid1 patients N=120	N (%)	Healthy N=60 N (%)
sex			
male	68	(56) %	32 (53.3) %
female	52	(44) %	28 (46.6) %
Median age	63 (14-72) 60(15-69)		
≥15	3	(2.5) %	2 (3.33) %
16-30	20	(16.6) %	9 (15) %
31-45	27	(22.5) %	12 (20) %
46-60	39	(32.5) %	22 (36.6) %
≤60	31	(25.8) %	15 (25) %

This study illustrated that male more incidence with covid-19 than female , this in line with (Raimondi *et al.*,2021) found that male was (72.4% vs 27.6%), with a male/female ratio of 2.6:1 and mean age of patients was (67.0 ± 14.5) years . In local study, AL-Najaf -Iraq , Abd-Alamear,(2021)revealed that Covid 19 pneumonia patients male recorded 27 (54%) and female were 23 (46 %) . Also in Basra-Iraq , (Ad'hiah *et al.*, 2020) found that males outnumbered females in cases (60.4 vs. 39.6%) in 1014 Iraqi hospitalized cases during the period from May - July , 2020. gender differences play an important role in affecting the immune system function, and therefore , men are generally thought to produce a lesser amount of type I IFNs , inflammatory cytokines and possess a lower number of circulating T cells (Klein *et al.*, 2016). Other explain was the estrogen promotes both innate and adaptive immunity, while testosterone (a male hormone) in its turn has a suppressive effect on immune function.

In respect to age study in Baghdad - Iraq (Ad'hiah *et al.*, 2020) they demonstrated that age might be important risk factors for COVID-19 mean age of patients reach to fifth decade (48.2 ± 13.8 year), and 48.3% of patients were classified in the age group ≥50 years. It seems that the elderly more susceptible to COVID-19 and this hypothesis can be interpreted due to the reduction in number and size of ciliated cells of airway and decreased nasal resistance in elderly .

IL-10 concentration in Covid-19patients patients and healthy

The results indicated that IL-0 has been increased in the serum of Covid19 pneumonia patient's to (48.76 ± 12.3) pg / ml in compared with healthy controls (5.47±1.33) pg/ml in a significant difference (p-value ≤ 0.05) as shown in Figure (1)



Figure(1) IL-10 serum level in Covid-19 patients and healthy

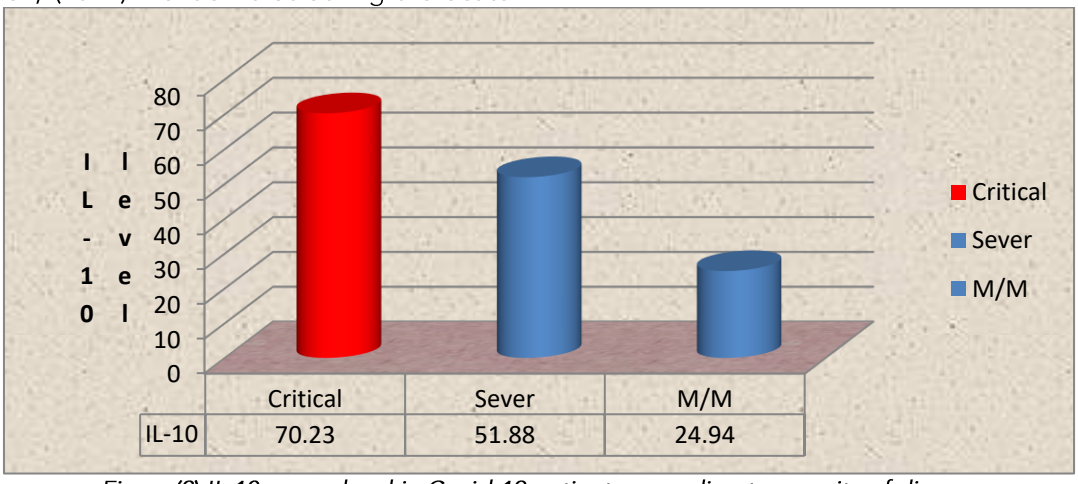
Cytokines play an important role in immunity and immunopathology during viral infections (Majeed *et al.*, 2022). This results found increased serum IL-10 cytokine in consist with study in Baghdad –Iraq by(Kathim et al., 2021) whom reported that IL-10 serum level was significantly elevated in COVID-19 patients as compared with healthy control (38.18±4.57 v.s.31.84±3.19 pg/ml) . Also (Gong *et al.*, 2020) they found that covid-19 patients have higher IL-10 concentration than healthy control group (7.67 ± 3.15 , 4.9 ± 1.6 pg/ml) . Similar results observed by (Wang *et al.*, 2020) who appeared that COVID-19 patients increased in anti-inflammatory cytokines such as IL-10 and IL-4 and these elevation associated with viral load and lead to increased severity of disease .

Luporini *et al.*, (2021) confirmed that IL-10 was associated with age (p = 0.04) and severity of the disease (p = 0.05) and concluded that IL-10 which might provide valuable information on the COVID-19 severity and changes during the treatment process .

Rojas *et al.*, (2017) mention that during the acute course of viral infection, IL-10 inhibits the activity of T cells, NK cells and macrophages that, despite necessary for viral elimination, are also key factors inducing tissue damage. In same line (Liu *et al.*, 2020) they indicate that IL-10 levels predict poor outcomes in patients with COVID-19.

IL-10 act as anti-inflammatory cytokine to inhibit pro-inflammatory cytokine but elevated level of both IL-10 , IL-6 ,TNF-α and other cytokine and chemokines this mean that IL-10 fail to inhibit pro-inflammatory cytokines , this phenomena explain by (Grosick *et al.*, 2018) they illustrated that the potential escape of activated immune cells from IL-10's anti-inflammatory action (i.e., IL-10 "resistance") leading to over exuberant pro-inflammatory cytokine responses.

The results revealed that serum level of IL-10 was increased in critical and server cases (70+.23 ± 14.83 , 51.88 ± 19.75) pg/ml higher than M/M cases (24.94 ± 4.62) pg/ml with a significant different at (p≤ 0.05) , as show in figure (2).



Figure(2) IL-10 serum level in Covid-19 patients according to severity of disease

Huang, *et al.*,(2020) who noted that 2019-nCoV infection initiated increased secretion of T-helper-2 cytokines (IL4 and IL10) as part of the cytokine storm associated with severe respiratory symptoms. Also (Lv *et al.*, 2020) appeared that the mean levels of IL-10 were increased substantially in patients of

severe and critical groups (6.78 , 11.04 pg/ml) compare to mean of IL-10 in mild group (5. 50pg/ml). This result in line with (Lu *et al.*, 2020) they noted that dramatic elevation of IL-10 in severe/critically ill patients that associated with cytokine release syndrome and lead to progressive of COVID-19 patients state .

High levels of IL-10 were recorded in severe COVID-19 patients and found to be associated with the compensatory anti inflammatory response syndrome that may be responsible for a greater number of secondary infections (50%) and sepsis (100%) reported in survivors (Duan *et al.*, 2020).

Peripheral IL-10 concentrations were significantly higher in intensive care unit (ICU) COVID-19 patients compared to non-ICU patients and can predict poor outcomes in patients ((Diao *et al.*, 2020) whom suggested that the early and dramatic IL-10 elevation upon SARS-CoV-2 infection might instead play a detrimental pathological role in COVID-19 severity.

(Tian *et al.*, 2020) they found that elevated interleukin-10 (IL-10) was observed in patients with the severe form of the disease and suspected this may be related to compensatory anti-inflammatory response (CARS), which may be responsible for higher number of secondary infections (50%) and sepsis (100%) reported in non-survivors.

Detection of IL-10 "-1082 A/G gene polymorphism with allele frequency in Covid-19 patients and healthy

The results revealed that IL-10 gene distribution in Covid-19 was GG homozygous genotype frequency higher in Covid-19 patients (58.3%) when compared to the healthy controls (21.7)% . Homozygous genotype AA prevalent was significantly different between the control and patients, and approximately 24 (12)% in Covid-19 patients and 29 (48.3)% in the healthy controls as shown in Table (2).

Table (2): IL.10 polymorphism in Covid-19 patients and control

IL-10	Critical/sever N= 75	Moderate / M N=45	OR(95 % CI)	Relative risk	Productive factor	P-value
A/A	7 (9.3)%	17 (37.8)%	0.198 (0.0739 to 0.5345)	0.4118	2.400	0.0014**
G/A	12(16)%	14 (31.1)%	0.421 (0.1744 to 1.0197)	0.6886	4.792	0.0553 ns
G/G	56(74.7)%	14(31.1)%	6.526(2.8802 to 14.7883)	2.1053	2.381	0.000***
Allele frequency						
A allele	26	48	0.183(0.1015 to 0.3316)	0.4704	2.528	0.0001***
G allele	124	42	5.450(3.0159 to 9.8505)	2.1260	2.528	

*(P<0.05): significant , **or***(P<0.05) higher significant

This results confirmed that critical/sever recorded the GG was (74.7)% while in M/M was (31.1)% , AA genotype was (9.3)% and (37.8)% for Critical/server and M/M respectively . According to allele frequency G allele was 124 for Critical /server and 42 for M/M while A allele was 26 for patient and 48 for healthy as elucidate in Table (3) .

Table (3): IL-10 polymorphism in critical/Sever group with mild/moderate group patients

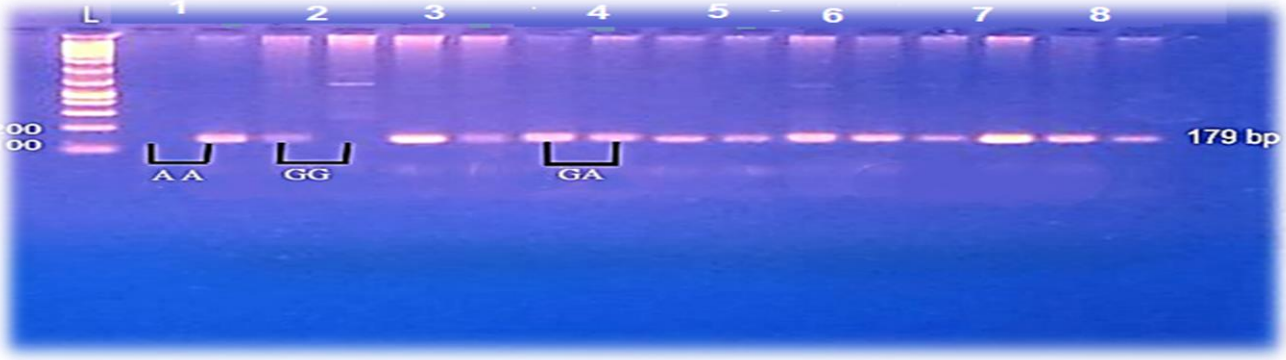


Figure (3): Ethidium bromide-stained agarose gel of PCR amplified 179bp of IL-10 gene in Covid-19 patients. L (ladder),for each patient there are two band , first represent G allele and the second band represent A allele (1,2 was AA genotype), (3,4 was GG genotype), (the remained was GA genotype), agarose gel 1%, 80 vol , 1 hour.

The results showed an association between the polymorphism of IL-10 gene and covid-19 infection the odds ratio for IL-10 gene -1082 G/A showed that the patients with genotype GG were susceptible to disease fifth time (5.061) than healthy and sixth (6.526) fold in critical more than M/M and allele G fifth (5.450) fold in patients than control group . From these data indicated that GG genotype consider a risk factor for covid-19 infection and for development and progression disease, these results were in accordance with the results by (Karcioglu -Batur and Hekim (2021) stated that individuals with GG genotypes showed a 1.73-folds higher risk of severity due to COVID-19 infection and frequency of AG genotype occurrence was lower in severe cases (30.7%) as compared to

mild cases (44.7%). Surpan *et al.*, (2022) observed that higher G allelic distribution and AG heterozygous genotype of the IL-10 gene in Covid-19 patients when compared to controls also demonstrated that prognosis, survival in resected SARD patients were strongly associated with the IL-10 haplotype. Similar results was founded by (Gallagher *et al.*, 2019) who found that GG genotypic frequency is significantly higher in Community acquired pneumonia (CAP) patients when compared to the controls, with a 1.6-fold risk for the disease , also, allelic frequency of G in CAP patients was significantly higher when compared to the healthy controls. Also (Schaaf *et al.*, 2003)whom found that patients suffering from Acute Respiratory Distress Syndrome possess the - 1082GG genotype that associated with increased serum level of IL-10 with severity of sepsis and mortality.

In other hand (Diao *et al.*,2020) they reported IL-10 is an inflammatory cytokine whose concentration was found to increase in patients that develop severe/critically ill condition post COVID-19 infection and observed that the heterozygous AG genotype was nearly significantly associated with decreased risk of disease severity (p = 0.068) whereas, a significant association of GG genotype was observed with severity of COVID-19 (p > 0.05) .

(Rizvi *et al.*, 2022) they observed that patients with the GG genotype, the frequency of severe sepsis (54.5%) was significantly higher than in patients with the AG (28.9%) and AA genotypes (7.8%). AA genotype was protective against severe sepsis ,the genotype distribution in patients who admitted to the ICU during their hospital stay were as follow: AA genotype (9.8%), AG genotype (34%), and GG genotype (63.6%). The GG genotype carried the risk of ICU admission and AA genotype was protective factor (P=0.0002) , also reported that the hospital mortality was in significant association with the GG genotype (36%), while AG and AA genotypes were not (7.8% and 1.9%, respectively). The AA genotype was protective against hospital mortality.

This results also illustrates that homozygous GG gene gives high production of IL-10, homozygous AA gives low production of IL-10, finally heterozygous AG genotype gives intermediate production of IL-10 As show in Table (**2**)

Table (2): serum level of IL-10 according to genotype variation in Covid-19 patients and healthy

	Serum level	GENOTYPE		
	Mean ± S.D	AA	GA	GG
Patient s	48.7 + 12.3	30.4± 5.3	33.7±11.2	80.6+ 16.3
Healthy	5.47 + 1.33	3.9+0.8	5.1+ 1.7	8.3+ 2.5
Significantly	P < 0.001			

Polymorphisms in the promoter regions of cytokine genes affect their production, thereby affecting the circulating levels in the plasma . (Suárez *et al.*, 2003) reported that 50–75% of the variation in IL-10 production is genetically controlled and according to IL-10 gene, a G to A single nucleotide promoter polymorphism at position -1082 is important in the regulation of IL-10, individuals homozygous for the G allele (-1082GG) have higher circulating IL-10, higher expression of IL- 10 mRNA, and greater production of IL-10 after in vitro stimulation .

(Galley *et al.*, 2003) who reported that individuals carrying GG genotype have increased levels of IL-10 transcription and higher concentrations of circulating IL-10 as compared to AA genotype carriers . This results agree with (Tai *et al.*, 2020)they reported that G to A polymorphism at −1082 position regulates transcription of IL-10 gene , high levels of IL-10 were recorded in severe COVID-19 patients and found to be associated with the compensatory anti-inflammatory response syndrome that may be responsible for a greater number of secondary infections (50%) and sepsis (100%) reported in survivors

Wang *et al.*,(2020) they explain that IL-10 gene polymorphism is strongly associated with COVID-19 severity and AA genotype confer a protective role in preventing severe disease progression. (Karcıoğlu Batur and Hekim, 2021) that observe the -1082GG genotype is associated with the development and outcomes in ARDS and confirmed that GG genotype associated with increase production of IL-10 systemically and locally .

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