ORIGINAL RESEARCH PAPER

General Medicine

"HIGH SENSITIVITY C-REACTIVE PROTEIN AS A PREDICTOR OF DISEASE PROGRESSION IN NAÏVE HIV PATIENTS"

KEY WORDS: HIV, CD4, hsCRP and opportunistic infection.

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ABSTRACT

Human immunodeficiency virus (HIV) infected persons, compared with HIV-negative people have a higher risk of developing a opportunistic infection. In HIV/AIDS, plasma HIV-1 RNA concentration reveals the degree of viral replication, and CD4 counts reflect the degree of immune deficiency and end-organ damage. The viral load and CD4 counts are established as diagnostic gold standards for HIV, soluble markers may indicate some information about immune activation status and prognosis.

In researches hsCRP(High sensitivity C-reactive protein) is considered to be a potential biomarker for anticipating long-term disease progression and cardiovascular disease (CVD) risk, which is also one of the major long-term complications in HIV patients. Moreover it is also considered to be a marker for predicting mortality and as a guide for routine monitoring of disease activity with a potential to replace traditional costlier measures such as CD4 count and HIV RNA load.

Opportunistic infections in people living with HIV reflect the immune suppression of the host. Hence, CRP can be used as a marker of degree of immune suppression. The cytokine profile found with raised CRP levels is predominantly pro-inflammatory, and CRP levels are often used as a non-specific indicator of inflammatory activity, irrespective of the cause. High sensitivity CRP is a reliable marker of disease progression and may prove to be a cheaper alternative for routine disease monitoring and predicting HIV-related outcomes, especially in a resource- poor setting.

INTRODUCTION

Human immunodeficiency virus (HIV) infected persons, compared with HIV-negative people have a higher risk of developing a opportunistic infection and previous data indicate a high morbidity and mortality, associated with this entity. The clinical symptoms of infections are often non-specific and confirming the presence of infection is difficult. The early confirmation of infections is particularly problematic among immunocompromised patients such as those who are HIV infected.[1]

In HIV/AIDS, plasma HIV-1 RNA concentration reveals the degree of viral replication, and CD4 counts reflect the degree of immune deficiency and end-organ damage. The outcome is, however, largely influenced by the co-existence of other complications, especially co-infection like TB. The viral load and CD4 counts are established as diagnostic gold standards for HIV, soluble markers may indicate some information about immune activation status and prognosis. Levels of acute phase protein as markers of inflammation usually rise markedly during acute and chronic infections.[2]

C-reactive protein (CRP) is one of the marker most commonly used, with varying degrees of success, as diagnostic or prognostic indicators to monitor disease progression and to estimate the efficacy of therapeutic interventions in infectious diseases and non- infectious inflammatory conditions.

C-reactive protein (CRP) is an acute-phase protein and is established as a nonspecific marker of systemic inflammation. In HIV-seropositive patients it is increased in both pneumococcal community acquired pneumonia (PCAP)[3] and pulmonary tuberculosis (PTB).[4] Its levels are upregulated in viral, bacterial and fungal infections, as well as in non-infectious inflammatory conditions. In researches hsCRP is considered to be a potential biomarker for anticipating long-term disease progression and cardiovascular disease (CVD) risk, which is also one of the major long-term complications in HIV patients. Moreover it is also considered to be a marker for predicting mortality and as a guide for routine monitoring of disease activity with a potential to replace traditional costlier measures such as CD4 count and HIV RNA load.[5]

CRP levels increase with infection and there exists a negative correlation between CRP and CD4 count.[6] Opportunistic infections in people living with HIV reflect the immune suppression of the host. Hence, CRP can be used as a marker of degree of immune suppression. The cytokine profile found with raised CRP levels is predominantly pro- inflammatory, and CRP levels are often used as a non-specific indicator of inflammatory activity, irrespective of the cause.[7] The macrophage and perhaps adipocyte-derived IL-6 which is acute phase reactant acts as a major stimulant for the production of CRP, and liver failure is the major cause for a decline in CRP synthesis.[8,9]

Very few studies have been performed in India on hsCRP treatment naïve HIV patients; therefore present study is an effort to evaluate correlation as well as association between CD4 count and early infection and hsCRP levels in HIV patients. The aim of this investigation was to compare the associations of C-reactive protein and measures of HIV disease status in treatment naive HIV patients.

METHODOLOGY

This is a hospital based observational cross sectional study conducted in Medicine Wards and ART Centre of SMS Hospital, Jaipur. Sample size of 30 patients is taken in each group.

Inclusion Criteria:

1. Treatment naïve HIV positive patients.
2. Age >18 years.

Exclusion Criteria:

1. Patients with Pre-existing sepsis.
2. Pre-existing cardiovascular disease,pre-existing liver dysfunction and pre-existing renal dysfunction.
3. Who are not willing to give consent.

Data regarding patient's history and clinical information were collected in a prestructured pro forma. Basic investigation like CBC, blood sugar, renal function test,liver function test, chest X-ray and CD4 count was done at the baseline. Details

regarding HIV infection were also collected with respect to mode of infection, duration of illness, clinical signs and symptoms, WHO staging of the disease, presence of opportunistic infections. Suitable investigation was performed as per clinical indication.

OBSERVATION

This is a hospital based observational, cross sectional study with 50 subjects who were diagnosed as HIV infected by ELISA rapid and simple (ERS) test according to NACO guidelines between June 2018 and November 2019, and who presented to the Department of General Medicine, S.M.S Hospital & Attached Group of Hospitals, Jaipur and were treatment naïve.

Table : Demographic and Blood investigation in cases and controls

Parameter	Cases	Controls
Age	39.2±9.7 years	36.6±16.2 years
Gender (M/F)	34/16	33/17
Hb (g/dl)	11.8±1.45	11.9±1.6
TLC (×10^{3}cells/µl)	5.6±1.6	6.6±1.7
DLC(N) (% of TLC)	61.8±3.7	65.6±5.0
DLC(L)(% of TLC)	29.6±3.3	28.±3.4
ESR (mm/1st hr)	42.7±32.2	20.8±7.83
Billirubin (mg/dl)	0.8±0.2	1.0±0.4
SGOT (U/L)	33.8±12.8	31.9±7.9
SGPT (U/L)	29.7±12.8	26.6±8.7
Albumin (g/dl)	3.4±0.5	3.6±0.3
Urea (mg/dl)	22.4±5.9	25.4±7.4
Creatinine (mg/dl)	1.0±0.2	1.0±0.2

The mean age of patients was 39.2±9.7 years in cases and 36.6±16.2 years in control. The majority of patients (34%) were in age group 31-40 years followed by 30% in 41-50 years, 22% were in 21-30 years, and 14% were in age group greater than 50 years. Similarly, in controls majority of patients (24%) were in age group 21-30 years and 31-40 years respectively followed by 20% in >50 years, 18% were in age group 18-20 years, 14% were in age group 41-50 years, and 12% in >50 years. Here, ESR, SGOT and SGPT were significantly different in cases and control and other were non-significantly different.

Table: Blood investigation in cases according to CD4 count

	MEAN±SD		P-value
	CD4 ≤ 200 (cells/µl)	CD4 >200 (cells/µl)	(unpaired T-test)
Hb (g/dl)	11.3±0.96	12.01±1.5	>0.05
TLC (×10^{3}cells/µl)	5.41±1062	5.7±1.5	>0.05
DLC(N) (% of TLC)	61.3±3.6	62±3.7	>0.05
DLC(L) (% of TLC)	29.63.5	29.5±3.2	>0.05
ESR (mm/1st hr)	50.5±30.6	38.2±36.6	0.001
Billirubin (mg/dl)	0.77±0.26	0.8±0.2	>0.05
SGOT (U/L)	30.8±13.7	35.4±13.2	0.031
SGPT (U/L)	26.4±13.1	31.5±12.5	0.027
Albumin (g/dl)	3.3±0.57	3.4±0.45	>0.05
Urea (mg/dl)	21.8±5.6	22.7±6.1	>0.05
Creatinine (mg/dl)	0.91±0.17	1.0±0.2	>0.05

Here, ESR, SGOT and SGPT were significantly different in patients having CD4 count >200 cells/µl as compared to patients having CD4 count ≤ 200 cells/µl.

Table :Mean of HsCRP in cases and controls

	CASES	CONTROLS	P-value (unpaired t-test)
HsCRP (mg/l)	13.3±18.9	0.78±0.56	0.0001

The mean HsCRP in cases was 13.3±18.9 mg/l and in controls it was 0.78±0.56 mg/l. The difference was statistically significant with p value 0.001.

Table: Aassociation between HsCRP, CD4 levels with opportunistic infections in HIV cases

	HIV cases with Opportunistic Infections (N=20)		HIV cases Without Opportunistic infections(N=30)		P-value (unpaired t-test)
	Mean	SD	Mean	SD	
HsCRP (mg/l)	25.1	25.1	5.5	5.1	0.0001
CD4 (cells/µl)	199.1	144.4	314.1	120.8	0.0001

In patients having opportunistic infections mean HsCRP was 25.1±25.1 mg/l and CD4 count was 199.1±144.4cells/µl. In patients without opportunistic infections mean CRP was 5.5±5.1 mg/l and mean CD4 count was 314±120.8cells/µl.The difference was statistically significant with p-value less than 0.005.

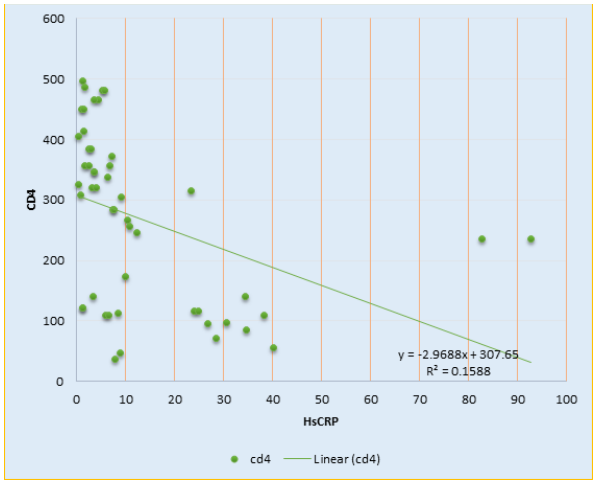

Fig 1: Pearson's Correlation of HsCRP and Cd4

Here we found a significant Pearson's Correlation between CD4 count and HsCRP and Albumin and HsCRP.

DISCUSSION

Our study assessed the value of inflammatory markers such as TLC, DLC, ESR,Albumin, and hsCRP in treatment naive HIV positive patients and in healthy controls. Total 50 treatment naive HIV positive cases and 50 healthy controls were taken in the study.

In our study the mean age of cases was 39.2±9.7 years and that of the controls was 36.6±16.2 years. Thirty four (68%) males and 16(32%) females were included in cases and 33(66%) males and 17(34%) females were included in controls. Mikula et al studied 15 females and 25 males as cases and 9 females and 28 males as controls with the mean age of patients was 34.5±8.8 years in cases and that was 39.7±8.9 years in controls [10]. In a study by Gahlot and Gahlot found that males were higher in study (76%) as well as control (64%) group than females as this disease affects males more because of heterosexual nature[11]. Similar proportion is reported by NACO, as females in PLHIV group being 40.5%[12].

In our study, cases and control were comparable on biochemistry and CBC analysis. The mean hsCRP in cases were 13.3±18.9 mg/l and in control were 0.78±0.56 mg/l. The difference was statistically significant with p value less than 0.05. Mean CRP in cases was 64.08±114.8 and in controls 2.3±5.4 mg/l. The value of mean hsCRP in cases in our study was lesser because we had taken treatment naive HIV patient as cases while they had taken HIV cases on ART.

In our study, in HIV cases having opportunistic infections, mean hsCRP was 25.1 mg/l and mean CD4 count was 199.1 cells/µl. In HIV cases without opportunistic infections mean

hsCRP was 5.5 and mean CD4 count was 314 cells/µl. All differences were statistically significant. Highest hsCRP level was found in tuberculosis (58.58 ± 31.5) followed by oral candidiasis, diarrhoea, wasting syndrome, lower respiratory tract infections, sexually transmitted disease and sepsis. In their study, Gahlot and Gahlot found that highest CRP level was for tuberculosis followed by oral candidiasis, lower respiratory tract infections and diarrhoea[11]. Kala Yadhav ML et al (2012) found that out of 86 tuberculosis patients, 23 had no history of treatment and CRP was found to be 41.2 mg/L[13].

Here in our study we found a positive significant correlation between PCT and CD4 count with r= 0.179 and p-value less than 0.05. And there was significant negative correlation between HsCRP and CD4 with r value=-0.3985 with p-value =0.001. Mikula et al[10] found that for HIV patients with HsCRP, CD4 count show significantly negative correlation with r=0.31. Gahlot and Gahlot[11] found that The CRP levels and CD4 count were negatively correlated in study group and this was observed to be statistically significant (p=0.04). Ugwu MC et al (2016) observed that the CRP levels and CD4 count were negatively correlated in study group and this was observed to be statistically significant (p=0.04) whereas in control group, the CRP levels and CD4 counts were found to be very weakly positively correlated and this correlation was also observed to be statistically insignificant (p=0.665)[14].

CONCLUSION

Our study also suggests an important role of quantitative CRP in diagnosis of opportunistic infections(OIs). When HIV patient is affected by OIs its quantitative CRP levels also increases. Different OIs have different levels of CRP such as highest hsCRP level was found in tuberculosis (58.58 ± 31.5) followed by oral candidiasis, diarrhoea, wasting syndrome, lower respiratory tract infections, sexually transmitted disease and sepsis. Severity of infection increases CRP level also increases in proportion. In our study patients have highest levels of CRP and patients with diarrhea and LRTI have lowest.

It can be safely concluded that HsCRP is an excellent predictor of infection in HIV patients.

Thus HIV-seropositive patients have significantly higher C-reactive protein levels than those with controls. High sensitivity CRP is a reliable marker of disease progression and may prove to be a cheaper alternative for routine disease monitoring and predicting HIV-related outcomes, especially in a resource- poor setting.

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