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The prognostic validity of affordable alternative biomarkers in HIV infection

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ABSTRACT

Background-Human immunodeficiency virus (HIV) infection is a global pandemic with varying prevalence in Indian states. Since 2010, north-eastern states have seen an increase in infections, and by March 2023, 1.68 million individuals were on antiretroviral therapy (ART). Routine evaluations of haematological and biochemical markers are carried out, but there is a need for more research on substitute markers related to HIV pathogenesis, patient vulnerability, and treatment responses, particularly focusing on affordable biochemical variables as alternative prognostic indicators in developing countries like India.

Methods- This observational and cross-sectional study was conducted at the Sir J.J. Group of Hospitals, Grant Government Medical College, Mumbai, in the Department of Biochemistry. This study involved 150 HIV-positive participants and 50 controls, totalling 200 subjects. The HIV-positive participants were categorized based on CD4 counts into three stages: Stage I (≥500 cells/µl), Stage II (201-499 cells/µl), and Stage III (≤200 cells/µl) having 50 subjects each. Blood samples were collected for serum total protein and other investigations, and were stored at -20 °C for analysis using autoanalyzer.

Results- In our study we noted that biochemical markers such as serum total protein, A/G ratio, and haemoglobin showed statistically significant alterations in HIV group as compare to control group. In progressive stages based on CD4 count modifications with striking significant correlation were observed between CD4 count and serum total protein and haemoglobin.

Conclusion-In rural areas, government health systems struggle with CD4 count and viral load assays for HIV. There is an urgent need for low-cost alternative indicators to monitor HIV progression. Indicators such as serum total protein and haemoglobin could serve as inexpensive substitutes when CD4 count is under 499 cells/µl in stage II. Regular monitoring of these biochemical markers may be suggested to improve prognosis, manage co-morbidities, and lower mortality rates.

Keywords: Human immunodeficiency virus, serum total protein, haemoglobin

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INTRODUCTION

AIDS is caused by the human immunodeficiency virus (HIV), a retrovirus with an encapsulated structure containing glycoprotein 160 and a viral envelope. It connects to CD4 cells and progresses through stages: acute, chronic, and AIDS. Antiretroviral medications, including NNRTI and NRTI, inhibit HIV replication and attachment through various mechanisms. The syndrome results in a gradual decline of the immune system, increasing susceptibility to cancer and opportunistic infections [1-4]. An individual diagnosed with HIV is infected for life. Effective and cost-efficient treatment is vital, especially in poorer nations with high HIV prevalence. This necessity highlights the importance of identifying low-cost prognostic indicators for AIDS and HIV, beyond traditional measures like CD4 cell count and viral load. While previous studies have explored certain biochemical markers such as serum albumin,serum highsensitive C reactive proteins,as economic prognostic tools, this study aims to evaluate the prognostic utility of more routine and inexpensive variables, including serum total protein, globulin, A/G ratio, random blood glucose, and hemoglobin in tracking HIV progression [5-6].

Methods

HIV infection weakens immunity, characterized by inflammation and metabolic dysregulation, making it crucial to understand these changes for informing HIV care and therapy. The present cross sectional,observational study was carried out at the biochemistry department of the Sir J.J. Group of Hospitals, Grant Government Medical College, Mumbai. The approval for the study from institute ethical committee was obtained. For the whole sample size of 200 people in the current investigation, 150 HIV-positive individuals and 50 controls were required. The sample size was established by means of 80% power value and 5% threshold of significance. A group of 150 people who tested positive for HIV were included in HIV group and categorised into Stage I- CD4 levels were defined as ≥500 cells/µl; Stage II- CD4 counts were 201-499 cells/µl; and Stage III- CD4 counts were ≤200 cells/µl having 50 subjects each. The appropriate containers were used to collect the blood sample needed for serum total protein and related tests like haemoglobin and random blood sugar. The separated serum and plasma were kept at -20 °C in appropriately labelled Eppendorf containers before being estimated on an autoanalyzer using diagnostic kits. Statistical analysis was conducted using SPSS Software 20.0

Discussion

An HIV infection is an important cause of disease worldwide, and since the inception of AIDS, the impact on the human population has been of great magnitude. Establishment of ART prevents the progression of the disease, prolongs survival, improves quality of life, and reduces the onset of opportunistic infections. Laboratory test findings, such as rising plasma HIV viral load and falling CD4+ T cell counts, are non-clinical markers of disease progression. Underdeveloped and developing countries at a standstill boast a financial crunch to acquire infrastructure and scientific technology for performing such tests regularly. The said attempt was made to assess the role of different alternative low - cost biochemical parameters, in the progression of HIV infection. In this study we observed that, the mean serum total protein level of the control group was 7.418±0.259 g/dl and in HIV group, it was significantly decreased to 7.018±0.566 g/dl (p value<0.001). However, serum globulin level in the HIV group (3.246±0.308 g/dl) was significantly increased as compared to the control group (2.924±0.167 g/dl) (p value<0.001) and further, calculated Albumin/globulin ratio in HIV group 1.177±0 was significantly decreased as compared to control group 1.541±0.118 (p value<0.001). It was seen that, random blood glucose level in the HIV group was significantly increased (106.528±31.102 mg/dl) as compared to the control group (96.020±5.971 mg/dl). (p value<0.05). The haemoglobin level in the HIV group significantly decreased to 12.862±1.739 gm/dl as compared to the control group, 14.464±1.192 gm/dl. (p value <0.001) (Table-1).

Table 1: Biochemical marker levels from the HIV and control groups

Laboratory Investigation	HIV Group	Control Group	Independent T test	P-value
	Mean± SD	Mean± SD		
Serum Total Protein gms/dl	7.018±0.566	7.418±0.259	4.827**	<0.001
Serum Globulin gms/dl	3.246±0.308	2.924±0.167	7.052**	<0.001
A/G ratio	1.177±0.256	1.541±0.118	9.700**	<0.001
Random plasma glucose mg/dL	106.528±31.102	96.020±5.971	2.371*	0.019
Haemoglobin g/dL	12.862±1.739	14.464±1.192	6.052**	<0.001

**Statistically Significant at 5% level i.e. P<0.05.*

We observed, serum total protein level was significantly decreased from Stage I CD4 count ≥500 to Stage II CD4 count 201-499 and Stage III CD4 count ≤200. These levels were significantly decreased in the Stage III CD4 count <200 group when compared to CD4 Count 201-499, CD4 Count ≥500, and Stage II CD4 count 201-499 to Stage I ≥500 (p value<0.001).

Serum globulin level was significantly decreased from Stage I CD4 count ≥500 to Stage II CD4 count 201-499 and CD4 count ≤200. These levels were significantly decreased in the Stage III CD4 count ≤200 group when compared to Stage II CD4 count 201-499 (p value<0.05) along with Stage I CD4 count ≥500 (p value<0.001). However, when compared to Stage II CD4 count 201-499 to >500, it seems non-effective.

The albumin/globulin ratio was significantly decreased from Stage I CD4 count ≥500 to Stage II CD4 count 201-499 and Stage III CD4 Count ≤200. These levels were significantly decreased in the Stage III CD4 count ≤200 group when compared to CD4 Count 201-499, CD4 Count >500, and Stage II CD4 count 201-499 to ≥500 (p value<0.001).

Further, it was noted that, random blood glucose levels were significantly decreased from a Stage I CD4 count ≥500 to a stage II CD4 count of 201-499 and stage III CD4 count <200. These levels were significantly decreased in the Stage III CD4 count ≤200 group when compared to Stage II CD4 count 201-499 (p value 0.990), along with Stage I CD4 count ≥500 (p value <0.05), and when compared to Stage II CD4 count 201-499 to stage I ≥500 (p value <0.05).

Haemoglobin level was significantly decreased from Stage I CD4 count ≥500 to Stage II CD4 count 201-499 and stage III CD4 count ≤200. (p value<0.001) These levels were significantly decreased in the Stage III CD4 count <200 group when compared to Stage II CD4 count 201-499 (p value<0.05) and Stage I CD4 count ≥500 (p value<0.001). However, when compared to Stage II CD4 count 201-499 to stage I ≥500, it seems non-effective. (p value: 0.087) (Table-2)

Table 2: Biochemical marker levels at different stages of HIV based on CD4 count (contd.)

Level of CD4 cells/µl	HIV Group Mean± SD		F test (ANOVA)	P-value	Post hoc Sig.
Random plasma glucose mg/dL					
Stage III ≤200	100.464±12.102		5.253*	0.006	Yes
Stage II 201 – 499	101.280±14.280				
Stage I ≥500	117.840±48.937				
Post-Hoc Test; Tukey HSD; If F test -Sig	CD4 count Level	Mean diff	P-Value	95% CI	
Stage III ≤200	Stage II 201 – 499	-0.8160	0.990	-15.141	13.509
Stage III ≤200	Stage I ≥500	-17.3760	<0.05	-31.701	-3.051
Stage II 201 – 499	Stage I ≥500	-16.5600	<0.05	-30.885	-2.235
Haemoglobin g/dL					
Stage III ≤200	12.016±1.388		12.518	<0.05	Yes
Stage II 201 – 499	12.940±1.459				
Stage I≥500	13.630±1.950				
Post-Hoc Test; Tukey HSD; If F test -Sig	CD4 Level	Mean diff	P-Value	95% CI	
Stage III ≤200	Stage II 201 – 499	-0.9240	<0.05	-1.6904	-0.1576
Stage III ≤200	Stage I ≥500	-1.6140	<0.05	-2.3804	-0.8476
Stage II 201 – 499	Stage I ≥500	-0.6900	0.087	-1.4564	0.0764

**Statistically Significant at 5% level i.e. P<0.05.*

To know the more precise role of the above variables in HIV progression, we correlated CD4 count with biochemical markers under study.

Correlation coefficient and CD4 count with various biochemical markers

We observed that CD4 count and serum total protein (p<0.001; r = 0.694), serum albumin (p<0.001, r = 0.797), A/G ratio (p<0.001, r = 0.720). were positively correlated and statistically highly significant. whereas CD4 count with serum globulin was negatively

correlated and statistically highly significant (p<0.001, r = -0.283). CD_4 count with random blood glucose was positively correlated and statistically significant (p<0.05, r = 0.245). Whereas from liver indices, CD_4 count with serum total bilirubin was negatively correlated and statistically non-significant (p 0.557 r = -0.048). While, CD_4 count with haemoglobin was positively correlated and statistically significant (p 0.001 r = 0.342).

Table 3: Correlation coefficient-CD_4 count with various biochemical markers

Parameters	Pearson Correlation	Sig. (2-tailed)
CD_4 Count cells/µl	1.000	-
Serum Total Protein gms/dl	.694**	.001
Serum Globulin gms/dl	-.283**	.001
A/G ratio	.720**	.001
Random plasma glucose mg/dL	.245**	.003
Haemoglobin g/dL	.342**	.001

***Correlation is significant at the 0.01 level (2-tailed).*

Correlation coefficient: CD_4 count stage wise with various biochemical markers

Here, we observed that CD_4 count (stage I ≥500) and serum total protein were negatively correlated and statistically non-significant (p 0.763, r = -0.044). Serum globulin was negatively correlated (p 0.869, r = -0.024) and albumin/globulin ratio were positively correlated (p 0.919, r = 0.015). In our study, we observed that CD_4 count (stage II 201-499) with serum total protein (p<0.01, r = 0.366) A/G ratio p<0.01, r = 0.366) were positively correlated and statistically significant. Whereas serum globulin was negatively correlated and non-significant (p 0.553, r = -0.086). Here in this, we observed that CD_4 count (stage III ≤200) with serum total protein (p<0.01, r = 0.571) serum globulin (p<0.05, r = 0.341) were positively correlated and statistically significant .CD_4 count (stage III ≤200) with albumin/globulin ratio was positively correlated (p 683, r = 0.059) but non-significant.

Table 4: Correlation coefficient and CD_4 count stagewise with various biochemical markers

	Pearson Correlation	Sig. (2-tailed)
CD_4 Count cells/µl(Stage III ≤200)	1.000	-
Serum Total Protein gms/dl	.571**	.001
Serum Globulin gms/dl	.341*	.015

A/G ratio	.059	.683
Random plasma glucose mg/dL	-.397**	.004
Haemoglobin g/dL	.303*	.033
CD4 Count cells/µl(Stage II 201-499)	1.000	-
Serum Total Protein gms/dl	.366**	.009
Serum Globulin gms/dl	-.086	.553
A/G ratio	.366**	.009
Random plasma glucose mg/dL	-.035	.809
Haemoglobin g/dL	.231	.107
CD4 Count cells/µl(Stage I ≥500)	1.000	-
Serum Total Protein gms/dl	-.044	.763
Serum Globulin gms/dl	-.024	.869
A/G ratio	.015	.919
Random plasma glucose mg/dL	.078	.592
Hemoglobin g/dL	-.226	.115

***Correlation is significant at the 0.01 level (2-tailed).*
**Correlation is significant at the 0.05 level (2-tailed).*

The pathogenesis of hypoalbuminemia in HIV infection is multifactorial, stemming from poor nutrition, chronic inflammation, anorexia, cytokine regulation, and aberrant immune activation. Key factors include hypergammaglobulinemia, reversal of the A/G ratio, and autoantibodies against serum albumin, alongside hepatic and renal involvement. These factors significantly affect serum total protein, albumin, globulin, and the A/G ratio, with chronic inflammatory states leading to hypoproteinaemia, particularly through albumin leakage due to increased capillary permeability. [7]

Our findings are in similar lines with earlier studies by Kandi Venkataramana (2013) Mrs. Pawar Meena Shivaji (2018) Bhattacharyya SK (2018) Vandana Balgi (2019) Nitin Mehta (2024). [8-12] CD4 count (stage I ≥500) with random blood glucose was positively correlated (p 0.592, r = -0.078). CD4 count (stage II 201-499) with random blood glucose was negatively correlated (pp 0.809 r = -0.035). CD4 count (stage III ≤200) with random blood glucose was negatively correlated and statistically significant (p<0.05, r = -0.397). Socio-cultural, lifestyle, behavioural, anthropometric, metabolic, and endocrine factors all influence glucose metabolism. Prolonged exposure to ART can elevate the risk of metabolic abnormalities, including lactic acidosis, osteopenia, dyslipidaemia, and disorders related to glucose metabolism. Our observations are near to the previous studies

carried out. [13-15]. Also, CD_4 count (stage I ≥500) with haemoglobin was negatively correlated and statistically nonsignificant ($p = 0.115$, $r = -0.226$). CD_4 count (stage II 201-499) with haemoglobin was positively correlated and statistically significant ($p = 0.107$, $r = 0.231$). Whereas CD_4 count (stage III ≤200) with haemoglobin was positively correlated and statistically significant ($p < 0.05$, $r = 0.303$). The low haemoglobin and red blood cell count in HIV-infected individuals may result from reduced red blood cell production, lower erythropoietin levels, and ineffective erythropoiesis. Few studies have focussed on and showing comparable observations. [16-19]. Significant correlations were observed in the study, but it has limitations due to the lack of attention given to such studies in the literature.

Conclusion

In remote locations, the government health system has little control over the CD_4 count and viral load assays. Working on low-cost alternative indicators having promising potential for the development of HIV infection is highly required in the current situation. When HIV infection progresses, biomarkers such serum total protein and haemoglobin may be employed as routine, inexpensive, promising, such as when the CD_4 count is below 499 cells/µl in stage II.however larger sample size, uniform assessment methodology, longitudinal study period were the limitations of this study. It may be recommended to regularly evaluate these economical biochemical indicators to control co-morbidity, enhance prognosis, and reduce death rates.

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