Relation Between Clinical Profile, CD4 Count and Total Lymphocyte Count in *HIV* Infected Persons

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ABSTRACT

BACKGROUND

Total Lymphocyte Count has been advocated to predict CD4 count and to stage *HIV* disease in the absence of CD4 count. TLC is easily obtained by multiplying percentage lymphocytes by leukocyte count from routine complete blood picture with differential count. In light of its low cost and widespread availability, TLC has already been a useful tool in low-income countries for predicting immunosuppression and triggering opportunistic infection prophylaxis. Recent studies have also demonstrated that TLC alone and in combination with haemoglobin may be useful in determining as to when to initiate antiretroviral therapy. However, there are fewer studies examining the change of TLC in patients on antiretroviral therapy. Earlier studies exist on the usefulness of TLC as a surrogate for CD4 after HAART initiation but TLC has not found universal acceptance as a surrogate for CD4 counts. The latest WHO guidelines no longer recommend TLC as a guide to make treatment decisions in adults and adolescents.

METHODS

Data for the study was collected from inpatients and outpatients of King George Hospital, Visakhapatnam from December 2016 to September 2018 and from patients who were *HIV* positive. A total 50 patients were studied, out of which 38 were males and 12 were females. All the patients were clinically examined and subjected to relevant investigations including CD4 Count and TLC.

RESULTS

Males (38) outnumbered females (12) with the present study. There was no overall significant difference of mean age between male and female patients. Unprotected, multiple sexual contacts are the major risk factors for *HIV* infection. The common presenting symptoms were fever, anorexia, weight loss, lethargy, cough, diarrhoea and mouth ulcers. Most common opportunistic infections were tuberculosis, chronic diarrhoea and oropharyngeal candidiasis. CD4 Counts were less than 350 cells/µL in majority of patients who were symptomatic. The Total Lymphocyte Counts of 1750 cells/µL and 2450 cells/µL correlated to CD4 counts of 200 cells/µL and 350 cells/µL respectively.

CONCLUSIONS

There was a significant correlation between CD4 Count and Total Lymphocyte Count. TLC can be used as an effective laboratory tool to monitor disease progression in *HIV* infected persons where CD4 is not available and in resource poor countries.

KEYWORDS

Lymphocytes, CD4 Lymphocyte Count, *HIV* Infections

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BACKGROUND

Worldwide, approximately 30–36 million people are currently infected with human immunodeficiency virus (*HIV*). An estimated 1.8 to 2.3 million people succumbed to the acquired immunodeficiency syndrome (AIDS) in 2007 alone, including some 270 000 children. The global prevalence of *HIV* gradually increased from 29.8 million in 2001 to 36.9 million in 2014. The increase in *HIV* prevalence is mainly attributed to two factors - first, the *HIV* causes persistent infection till death as it creates permanent reservoir in memory TH cells, and the second factor is the availability of antiretroviral therapy (ART) that significantly improves the lifespan of PLH. Further, the occurrence of new *HIV* infections add up to the existing cases increases the PLH throughout the globe. Although the PLH are distributed worldwide, major proportion of them were living in the developing countries located in the southern Africa and Asia.

TLC is easily obtained by multiplying percentage lymphocytes by leukocyte count from routine complete blood picture with differential count. In light of its low cost and widespread availability, TLC has already been a useful tool in low-income countries for predicting immunosuppressant and triggering opportunistic infection prophylaxis. Recent studies have also demonstrated that TLC alone and in combination with haemoglobin may be useful in determining when to initiate antiretroviral therapy. However, there are fewer studies examining the change of TLC in patients on antiretroviral therapy. The purpose of this study is to assess the capability and clinical utility of TLC change to serve as a surrogate marker for CD4 count change in monitoring patients, which has important implications for resource-limited settings. As the incidence rate of *HIV* is increasing in India, the need for simpler and relatively accurate markers of disease progression through laboratory investigations are felt. We are correlating CD4 Count to Total Lymphocyte Count, which is available in all resource limited settings as it is obtained by multiplying Total Leucocyte Count and percentage of Lymphocyte in Differential Count, to monitor disease progression in *HIV* infected persons This dissertation is also an attempt to look into the correlation between opportunistic infections and progression of the disease, which is monitored by change in CD4 count and TLC. Since our study is being done in the resource poor set-up, the observations and conclusions can be used for monitoring progression of disease in *HIV* infected persons in our own set-up as well as other resource limited settings.

We wanted to determine whether the total lymphocyte count accurately predicts a low CD4 count in *HIV* infected persons and observe the clinical correlation between TLC and disease severity.

METHODS

This is a cross sectional descriptive study conducted among a total of 50 *HIV* positive patients who were admitted in King George Hospital, Vizag, Medical wards and those who visited Medical OPD from December 2016 to September 2018. Patients on cytotoxic drugs were excluded from the study. Using a pre-tested proforma, a detailed history was obtained from all the patients, who were included in the study. Further, as mentioned in the proforma detailed systemic examination followed by relevant investigations was conducted and results were noted. By multiplying the differential count of lymphocytes (DC) with Total leukocyte count (TC) and dividing by 100 Total lymphocyte count (TLC) was calculated.

(TLC = TC × DC lymphocyte/100)

For CD4 count <200 cells/μL and <350 cells/μL Sensitivity and specificity of various Total lymphocyte count cut-off were computed. As a diagnostic monitoring marker of benchmark changes in CD4 count, we evaluated changes in Total Lymphocyte count that indicates favourable response to ART. In the patients wherever necessary, who were symptomatic the following investigations were done. To find the significance of study parameters with variations with CD4 counts analysis of variance has been used .To find the correlation of CD4 counts with study parameters Pearson correlation co-efficient has been used.

F Test for K Population (Analysis of Variance)

Objective: K samples from K Populations with the same mean hypothesis is tested. Limitations: It is assumed that samples are independently distributed and also populations are normally distributed and have equal variance.

Significance of Pearson Correlation Coefficient

Objective: whether the difference between the sample correlation co-efficient and zero is statistically significant.
Limitations: It is assumed that the relationship is linear and vicariate normal distribution. Value of population co-efficient other than zero is assumed, and correlation co-efficient referred to as Z test.

Correlation Coefficient Classification

Trivial Correlation Up to 0.1 Small Correlation 0.1-0.3 Moderate Correlation 0.3-0.5. Large Correlation 0.5-0.7 Very Large Correlation 0.7-0.9 Nearly Perfect correlation 0.9- 1.0. Perfect correlation 1.0.

Statistical Software

The Statistical software namely SPSS 21 and Anova test were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

Between age group 31-40, 22 persons were observed, which constitutes 44%. Total number of females was 12 (24%) and total number of males was 38 (76%). The mean age of males was 41.38 yrs. and mean age of females was 35.45 yrs. (Table 1).

Age in Years	Male		Females		Total	
<30	5	13.1%	3	25%	8	16%
31-40	16	42.1%	6	50%	22	44%
41-50	12	31.5%	1	8.3%	13	26%
51-60	5	13.1%	1	8.3%	6	12%
>60	0	-	1	8.3%	1	2%
Total	38	100%	12	100%	50	100%
Mean± SD	41.1±10.0		35.5±8.5		40.0±10.0	

Table 1. Age and Sex Distribution

The major risk factor is heterosexual contact in males. Multiple heterosexual contact seen in 26 (72.2%) and history of multiple heterosexual contact and had also visited a STD Clinics observed in 9 (25.1%). Total number of females was 14 of which 6% (42.5%) their spouses were positive for *HIV*. History of multiple heterosexual contacts observed in 8 females of which 4 had also visited STD Clinic. No one has history of intravenous drug abuse. History of Blood transfusion was recorded in 1(2%) patients in male.

The most common opportunistic infection was tuberculosis amongst these patients is 27 (56%). Pulmonary Tuberculosis is seen in 13 patients only. Extra pulmonary Tuberculosis is seen in 14 and a combination of both Pulmonary and Extra pulmonary Tuberculosis is seen in 5%. Pleural Effusion, Tubercular lymphadenitis, Tubercular abdomen and Tubercular meningitis are the common forms of extra pulmonary Tuberculosis. Chronic diarrhoea caused by either Giardia lamblia or Entamoeba histolytica in 6 patients is the next commonest infection and in others the causative organism could not be identified. In 10 (20%) patients oropharyngeal candidiasis is seen, Pneumonitis is seen in 6 (12%) patients. In 2 patients (4%) skin infections, in 3 patients (6%) genital warts, in 1 patient (2%) Cryptococcal meningitis, in 1 patient (2%) Pericardial effusion, in 2(4%) herpes zoster and in 1(2%) patients PID is seen (Table -2).

Opportunistic Infection	Number (n=50)	%
Tuberculosis	27	54%
1. Pulmonary	13	26%
2. Extra pulmonary	14	28%
3. Both	5	10%
Chronic diarrhoea	16	32%
Oropharyngeal candidiasis	10	20%
Pneumonitis	6	12%
Skin infection	2	4%
Genital warts	3	6%
Pericardial effusion	-	-
Pelvic inflammatory disease	1	2%
Herpes zoster	2	4%
Cryptococcal meningitis	1	2%

Table 2. Distribution According to Opportunistic Infections

The CD4 counts were grouped under four different headings. i.e., <100 cells/µL, 101-200 cells/µL, 201-350 cells/µL and >350 cells/µL are the 4 different groups. The CD4 counts in 4 (8%) patients were less than 100/µL and in 16 (32%) patients between 101-200/µL, and in between 201-350/µL the number of patients is 22 (44%) and in 8 (16%) patients more than 350/µL are observed. 85 cells/µL and 90 cells/µL are the lowest CD4 count recorded in 2 patients who had Extra pulmonary tuberculosis. 850 cells/µL is the highest CD4 count recorded in a patient who was asymptomatic (Table -3).

The study parameters CD4 counts with Total count and total lymphocyte count show upward trend with p value of 0.0001 & 0.0001 respectively. Haemoglobin and ESR with CD4 counts, with their p values being 0.0001 & 0.068 respectively were also showing upward trend. To compare with the CD4 counts the Total Count, Total Lymphocyte Count, Haemoglobin and ESR were selected as study parameters (Table-4).

CD4 Count	Number	Percentage
<100	4	8%
101-200	16	32%
201-350	22	44%
>350	8	16%

Table 3. Distribution According to CD4 Count

Study Parameters Mean ± SD	CD4 Counts				Overall	p
	<100	101- 200	201-350	>350		
Total count	4835.33± 1483.36	4881.33± 2072.0	6101.33± 1816	9227.0± 4249.60	6089.0± 2784.01	0.0001
Total Lymphocyte count	1782.67± 383.5	1772.33± 685.4	1801.67± 453.9	2488.75± 1084.33	1891.33 ±696.74	0.0001
Haemoglobin	9.72± 1.16	11.25± 1.85	12.20± 1.80	11.90± 2.05	11.26± 1.86	0.0001
ESR	65±35.0	57±25.5	51±24.5	69±30.1	58±26.18	0.068

Table 4. Mean Pattern of Study Parameters with CD4 Counts

The Pearson Correlation for Haemoglobin with CD4 Counts was 0.45, at P <0.0001 and shows a moderate correlation between the two variables. The Pearson Correlation of Total Counts and Total Lymphocyte Counts and haemoglobin with CD4 Counts were significant (Table 5).

Study Parameters	Pearson Correlation	p value
Total count	0.45	0.0001
Total Lymphocyte count	0.45	0.0001
Haemoglobin	0.45	0.0001

Table 5. Pearson Correlation of Study Parameters

DISCUSSION

In the present study majority of patients were in the age group of 31-50 years, a total of 35, of which 28 were males and 7 were females. Thus Male to Female ratio was 4:1. According to the annual report of NACO 2015-16, in people infected with *HIV* the age group of 31-50 years was predominant, and Male to Female ratio was 3:2.[1] Whereas, Male to Female ratio in the findings of study by Kothari et al in 2001 was 5:1 and the age group 31-50 constituted 90%.[2] In a study conducted at a referral hospital in Calcutta by A. R. Sircar et al in 1998, the ratio was 3:1. By greater rate of exposure sexual practices, migration and other socio-economic factors, the differences were accounted for.[3]

The commonest mode of spread of *HIV* infection was Heterosexual transmission in the present study population which was similar to the findings in studies by A. R. Sircar et al (1998), and Kothari et al (2001).[2,3] Even in studies conducted by S. K. Sharma et al heterosexual transmission was the commonest mode of *HIV* acquisition. This is because; the commonest mode of disease transmission in India is multiple unprotected sexual contacts.[4] But, sexual contact among homosexual and bisexual men as well as intravenous drug abuse, has accounted for most of the cases

in the study conducted by American College of Physicians and Infectious Diseases Society of America (1993). This may be due to the differences between the two regions, in the socio-cultural perceptions and practices.[5] With a history of blood transfusion in our study, there was only 1 (2%) patient was presented, whereas in a study by A.R. Sircar et al (1998) 16.2% patients had history of blood transfusion.[3]

In our study number of patients with the CD4 counts less than 200 cells/µL were 20 (40%) patients. Tuberculosis, Chronic Diarrhoea and Oropharyngeal Candidiasis were the commonest opportunistic infections. The CD4 counts varied between less than 100 cells/µL to greater than 500 cells/µL, there was a significant relationship between the presence of pulmonary TB and low CD4 count. Incidence of extra pulmonary Tuberculosis increased over Pulmonary Tuberculosis as the CD4 count declined. With a CD4 count of 200-500 cells/µL, the risk of developing Pneumococcal and other bacterial Pneumonias, Pulmonary TB, Herpes zoster, Candidiasis, Kaposi's sarcoma was high. With a CD4 count less than 200 cells/µL the incidence of Pneumocystis carinii pneumonia, Disseminated Herpes simplex, Toxoplasmosis, Cryptococcosis, Miliary and Extra pulmonary Tuberculosis and Oro pharyngeal candidiasis was increased. At CD4 count less than 50 cells/µL disseminated Cytomegalovirus infection and Mycobacterium avium complex infection were common.

In our study, Total count and Total Lymphocyte Counts were showing positive trend to CD4 counts and were statistically significant. The Total Lymphocyte Counts of 1750 cells/µL and 2450 cells/µL showed similar observations to CD4 counts of 200 cells/µL and 350 cells/µL respectively. The p value was highly significant with Pearson Correlation of 0.45 for Total Counts (p value <0.0001) and 0.4 and total Lymphocyte Count (p value <0.0001).

In the study done by Beck E. J. et al at Academic Department of Public Health, St. Mary's Hospital Medical School, London, U.K. paired Total Lymphocyte Count and CD4 counts were taken from 1534 patients. A significant correlation between the above two parameters was noted, especially for patients with symptomatic *HIV* disease. This demonstrates the suitability of the use of Total Lymphocyte Count in the absence of CD4 count.[6] A study conducted by YRG Center for AIDS Research and Education, Chennai showed significant correlation between TLC of less than 1700 cells/µL and CD4 less than 350 cells/µL with p value of <0.01.[7] A study conducted by John Hopkins University showed a significant correlation between TLC of less than 1200 cells/µL to CD4 count of less than 200 cells/µL.[8] Whereas, study conducted in K. M. C. Manipal (2003) showed a that a significant correlation existed between TLC of less than 1200 cells/µL and CD4 counts of less than 200 cells/µL.[9] In our study CD4 count correlates to TLC better, when counts were less than 200 cells/µL (Table 6).

Apart from the studies mentioned above, R Wood, F Post and G Maartena (Department of Medicine, University of Cape Town Medical School, Anzio Road, Observatory 7925, Cape Town, South Africa) also studied the utility of CD4 counts and Total Lymphocyte Counts as predictors of *HIV* disease progression and concluded that for each clinical stage a significant difference in the progression to AIDS and mortality was predicted by Total Lymphocyte Count above or below 1250 cells/µL. Survival and progression to AIDS occurred at similar rates in patients with Total Lymphocyte Count of 1250 cells/µL or CD4 count of 200 cells/µL.[10] (Table 7).

Study Parameters	Studies	CD4 counts			
		<100	101-200	(201-350)	>350
Total Count	Our study	4835	4881	6101	9227
	John Hopkins study	4245	4355	5701	10891
	YRG study	4874	4935	5905	8975
Total Lymphocyte count	Our study	1782	1772	1801	2488
	John Hopkins study	1170	1250	1688	2260
	YRG study	1190	1205	1760	2870
Haemoglobin	Our study	9.72	11.35	12.20	11.90
	John Hopkins study	8.75	11.05	11.80	12.60
	YRG study	10.00	11.25	12.30	11.75

Table 6. Comparison of Mean Pattern of Study Parameters with CD4 Counts in Different Studies

Studies	Different Indices		
	Hb	TC	TLC
Our study	11.26	6089	1891
John Hopkins study	11.05	6298	1592
YRG study	11.325	6172	1756
Beck EJ study	11.316	6038	1298
KMC study (Manipal)	11.214	5270	1202
p value	0.0001	0.0001	0.0001
Pearson correlation	Significant	significant	Significant

Table 7. Comparison of Conclusions of Different Studies with CD4 of 200 Cells/µL

The pattern of CD4 counts over time is more important than any single CD4 count value. CD4 counts generally decrease as *HIV* progresses. Therefore it is more valuable to evaluate a series of CD4 counts than any single CD4 count. As the CD4 count is affected by the time of the day (lower in the morning), in acute illnesses, refrigeration of the blood sample (decreased CD4 count), with rough handling or contamination of blood sample, so the serial recording of Total Lymphocyte Count can give an equally stable reflection of progression of disease and development of AIDS in *HIV* infected persons.

Monitoring the patients with Total Lymphocyte Count has an enormous Cost Benefit in patients living in resource limited countries. The cost of TC and DC in standardized laboratories in India is Rs. 50 and CD4 count is Rs. 500. Though earlier studies exist on the usefulness of TLC as a surrogate for CD4 after HAART initiation. TLC has not found universal acceptance as a surrogate for CD4 counts. Akinola et al showed that TLC was not reliable predictor of CD4 cell count in *HIV* infected individuals.[11] The latest WHO guidelines no longer recommends TLC as a guide to make treatment decisions in adult and adolescents.

CONCLUSIONS

Majority of the patients with a CD4 count of less than 350 cells/µL had opportunistic infections. The Total Lymphocyte Counts of 1750 cells/µL and 2450 cells/µL correlated to CD4 counts of 200 cells/µL and 350 cells/µL respectively. Some

studies in developing countries observed the usefulness of TLC as a surrogate for CD4 after HAART initiation. There was a significant correlation between CD4 Count and Total Lymphocyte Count. TLC can be used as an effective laboratory tool to monitor disease progression in *HIV* infected persons where CD4 is not available and in resource poor countries.

REFERENCES

[1] National Aids Control Organization. Chap- 24. Annual report 2015-16. P. 336.

[2] Wadia RS, Pujari SN, Kothari S, et al. Neurological manifestations of *HIV* disease. The Journal of the Association of Physicians of India 2001;49:343-348.

[3] Sircar AR, Tripathi AK, Choudhary SK, et al. Clinical profile of AIDS: a study at a referral hospital. J Assoc Physicians India 1998;46(9):775-778.

[4] Sharma SK, Kadhiravan T, Banga A, et al. Spectrum of clinical disease in a series of 135 hospitalised *HIV*-infected patients from north India. BMC Infect Dis 2004;4:52.

[5] Dellit TH, Owens RC, McGowan JE, et al. Infectious diseases society of america and the society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clinical Infectious Diseases 2007;44(2):159-177.

[6] Beck EJ, Kupek EJ, Wadsworth J, et al. The use and cost of hospital services by London AIDS patients with different AIDS defining conditions. J Public Health Med 1996;18(4):457-464.

[7] Achhra AC, Zhou J, Dabis F, et al. Difference in absolute CD4+ count according to CD4 percentage between Asian and Caucasian *HIV*-infected patients. J AIDS Clin Res 2010;1(1):1-4.

[8] Sen S, Vyas A, Sanghi S, et al. Correlation of CD4+ T cell count with total lymphocyte count, haemoglobin and erythrocyte sedimentation rate levels in human immunodeficiency virus type-1 disease. Med J Armed Forces India 2011;67(1):15-20.

[9] Karanth SS, Rau NR, Gupta A, et al. Utility of total lymphocyte count as a surrogate for absolute CD4 count in the adult Indian *HIV* population: a prospective study. Avicenna J Med 2014;4(1):1-4.

[10] Post FA, Wood R, Maartens G. CD4 and total lymphocyte count as a predictor of *HIV* disease progression. QJM 1996;89(7):505-508.

[11] Akinola NO, Olasode O, Adediran IA, et al. The search for a predictor of CD4 cell count continues: total lymphocyte count is not a substitute for CD4 cell count in the management of *HIV*-infected individuals in a resource-limited setting. Clin Infect Dis 2004;39(4):579-581.