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ABSOLUTE LYMPHOCYTE COUNT: ALTERNATE MARKER FOR CD4 COUNT IN HIV POSITIVE PATIENTS IN RESOURCES RESTRAINED AREAS

Pathology

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ABSTRACT

BACKGROUND: All the HIV positive patients with progression of disease need HAART and prophylaxis against opportunistic infections. It is started when CD4 cell count falls below critical level. An alternate surrogate marker absolute lymphocyte count [ALC] is relatively cheaper investigation for monitoring HIV positive individuals. ALC is studied for its efficacy and its correlation with the CD4 count is established.

AIMS AND OBJECTIVES: We studied the correlation between CD4 count and ALC count. Also a critical value of absolute lymphocyte count (ALC) is found out at which there is maximum correlation with the CD4 count below 200/cmm is seen.

METHODS: The statistical analysis of correlation between CD4 count and ALC was done by Spearman's correlation coefficient. Also the diagnostic utility of change in ALC was evaluated as a marker of CD4 change by calculating the receiver operator characteristic (ROC) curves.

RESULTS: A total 1162 patients were studied. The ROC curve between ALC values and CD4 count of less than 200/micro liter showed significance (p value <0.05). Considering the optimum cut off value of ALC as 200/micro liter, an ALC value of 1459/cmm was derived which showed maximum correlation with sensitivity of 77.5% and specificity of 72.3%.

CONCLUSION: ALC has a positive correlation with CD4 count and is a useful surrogate marker for CD4 count. This surrogate marker can be used as parameter for starting HAART in non developed and developing countries and funds saved in costly investigations can be used to provide HAART to maximum patients.

KEYWORDS

HIV, CD4 count, Absolute Lymphocyte Count [ALC], HAART

INTRODUCTION:

The disease progress monitoring of Human Immunodeficiency Virus (HIV) infection / Acquired Immunodeficiency Syndrome (AIDS) is done with CD4 cell count and viral load. With the progression of disease CD4 count falls and patient become more prone for opportunistic infection. When CD4 count falls below 350/cmm or below 20%, Highly Active Anti Retro Viral Treatment (HAART) as well as prophylaxis for opportunistic infections should be started1. CD4 count and viral load estimation is done by more expensive modalities, like flow cytometry and polymerase chain reaction (PCR) which are not readily available in resource-limited settings.

In April 2002, WHO recommended that absolute lymphocyte count (ALC) can be used as an alternative marker to start antiretroviral therapy (ART) when CD4+ cell count is not available or is not affordable. Absolute lymphocyte count of less than 1,000-1,200 lymphocytes/cmm was recommended as a threshold to initiate ART[2].

The studies carried out for evaluating the relationship between ALC and CD4 count showed variable results with both good [3,4,5] and poor correlation [6,7,8,9].

The present study was done to assess correlation between CD4 count and absolute lymphocyte count in HIV-infected patients. A new threshold value of absolute lymphocyte count as an alternative to the recommended CD4 count threshold is also calculated. At this new threshold ALC value, maximum correlation with CD4 count is seen with CD4 count of <200/cmm.

SUBJECTS AND METHODS:

This was a prospective study done in Department of Pathology, at tertiary medical center which included patients registered in ART center in the duration of January 2014 to June 2014. A total 1162 patients were studied, with their clinical history, hematological findings and CD4 counts. Patients evaluated in the present study were from the 6 monthly follow up visit, when both CD4 counts and ALC were done. Those who are already taking ART were evaluated every 3 monthly so only first value of ALC and CD4 on the same sample is considered to avoid repetition. All HIV infected patients, registered with this ART center above 12 year of age from both sexes were included in the study. With universal safety precautions, 4 ml of venous blood was collected in a K3-EDTA vacutainers (k2 EDTA tube violet 2 ml, JK Diagnostics, Rajkot Gujrat, India) and it was processed for CD4 counts with the help of Flow Cytometer (BD FACSCalibur – Becton , Dickinson and Company, BD Bioscience, India). Absolute Lymphocyte Count was calculated with the help of cell counter (SYSMEX XS-800i) and peripheral smears.

STATISTICAL ANALYSIS -

The statistical analysis included two steps. In the first step of analysis correlation between ALC and CD4 count was calculated by Spearman's correlation coefficient and also by the coefficient of determination. A scatter diagram was plotted which depicted the relation between CD4 count and ALC. Sensitivity, specificity; positive and negative predictive values (PPV and NPV) were also calculated.

In the second step of the analysis, the diagnostic utility of change in ALC was evaluated as a marker of CD4 change. This was done by calculating the receiver operator characteristic (ROC) curves. With the help of ROC curve, a value of ALC at which maximum patients with CD4 count under 200/cmm was calculated.

RESULTS -

The study included total 1162 patients with age range of 12 to 66 year. The male: female ratio was 1:0.70. Both the mean and median age was 35 years (+/- 11years SD). The median value for ALC was 1753/cmm. The value of CD4 count was ranging from 6/cmm to 3766/cmm with median value of 360/cmm and standard error of mean of 8.016. A value of CD4% and ALC had significant correlation with coefficient of variance of 0.565 (Figure: 1).

There were 231 (19%) patients having ALC below 1200/micro liter and 931 (81%) patients above 1200/micro lit. A 257 (22%) patients were having CD4 count less than 200/micro liter while 905 (78%) were above it.

The ROC curve was drawn between ALC values and CD4 count values of less than 200/micro liter (Figure: 2). Area under the curve was 84% which was significant (p value <0.05). Considering the optimum cut off value of CD4 as 200/micro liter, an ALC value of 1459/cmm was derived which showed maximum correlation. Below the cut of value of ALC of 1459/cmm included maximum patients with CD4 count less than 200/cmm with sensitivity of 77.5% and specificity of 72.3%.

DISCUSSION -

In 1986, the first known case of HIV was diagnosed by Dr. Suniti Solmon in a female sex worker in Chennai. Since then number of HIV positive patient is on high and today India has the third highest number of estimated people living with HIV in the world10. According to the HIV estimations 2015, the estimated number of people living with HIV/AIDS in India was 2.17 million. According to The National AIDS Control Organization (NACO) technical report 2015, Maharashtra state is standing third with 0.31 million HIV patients [11].

First effective treatment regimen of retroviral disease was announced in 1996 since then the management has witnessed paradigm of changes. In the early era, ALC was used as an inexpensive, indirect marker of immunity status. With time, CD4 lymphocyte count and HIV RNA level has become standard for follow up of HIV patients and treatment.

The 2013 ART guidelines recommend initiating ART earlier i.e. at CD4 count ≤500 cells/mm3 and immediately irrespective of CD cell count for serodiscordant couples, pregnant women living with HIV, people with HIV and TB, people with HIV and hepatitis B, and children with HIV younger than five years[12].

The benefits of highly-active-antiretroviral therapy (HAART) are well documented. However, due to its high cost, people from developing countries currently have limited access to HAART. The overall cost for HAART is more than $1,000 per person per year[13].

The present study emphasises on use of absolute lymphocyte count as a predictive marker to start ART in resources restrained centres. S. Srirangaraj et al studied the usefulness of ALC in resource limited area in India and concluded that it is a good surrogate marker14. Akanmu et al stated that ALC correlates weakly with CD4 counts in patients undergoing antiretroviral therapy. ALC might get affected by many other factors and may not serve as a perfect surrogate marker for CD4 as a monitor of immunological response to therapy15. In our study, a positive ALC change is shown to be a sensitive and specific marker of positive CD4 change.

Following WHO guidelines, correlating CD4 count of less than 200/cmm and ALC value of less than 1200/cmm has sensitivity of 64.10%, specificity of 88.30%, PPV of 57.60% and NPV of 90.08%. If the value of ALC is increased to 1549/cmm, a fair sensitivity of 77.5% and specificity of 72.3% is noted. Increase in the cut off value for ALC will include more patients who will be benefited from early start of ART and prophylaxis for opportunistic infections. In 2002 Kumarsamy et al and in 2011 Kakkar et al studied the usefulness of ALC as a surrogate marker and found a good correlation[16,17].

Kumarsamy et al derived a value of 1400/cmm that can be used with sensitivity of 73%, specificity of 88%, PPV of 76%, NPV of 86% 16. However, some authors as Dashika et al in Fiji showed no correlation between CD4 and ALC 18. Reasons given by author regarding the same were small number of cases studied, inclusion of paediatric population and pregnant female who have different guidelines for ART. But author did find increase in CD4 count and ALC with starting of ART.

Badri et al concluded ALC value changes when patients are on ART and median change in CD4 count correlate with this change5. Adding other hematological parameters like hemoglobin, platelet count, hematocrit and coagulation profile would help us more in judging the time to start ART.

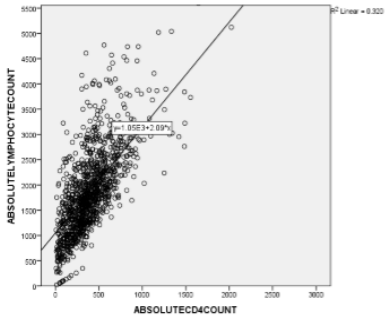

Figure.1: Scatter diagram showing relationship between ALC and CD4 count

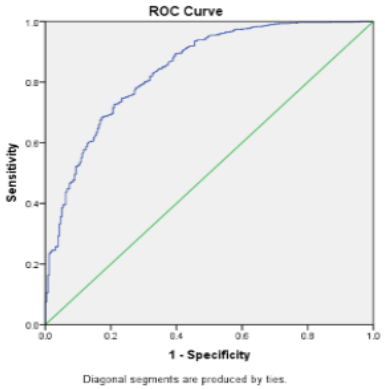

FIGURE 2: ROC curve showing lymphocyte count cut of value of 1459/cmm at which there is highest area under curve with sensitivity of 77.5% specificity of72.3%. Beyond this value there is trade off of sensitivity and specificity.

CONCLUSIONS -

In conclusion, ALC has a positive correlation with CD4 count and is a useful surrogate marker for CD4 count. The cut off value of ALC if increased to 1459/cmm, it will include maximum patients with CD4 count less than 200/cmm with fair sensitivity of 77.5% and specificity of 72.3%. This can be used in recourses restrained areas as a marker for starting ART and funds saved from expensive tests can be utilized for starting ART earlier.

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