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The Effect of cART on Neutrophil: Lymphocyte Ratio in HIV+ Patients Initiating Combined Antiretroviral Therapy

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Abstract: *Background:* Combined antiretroviral therapy (cART) has caused increased quality of life in Human immunodeficiency virus (HIV) positive patients and administration of this therapy comes with toxicity and possible inflammation. Neutrophil/Lymphocyte Ratio (NLR) is known to link with inflammation, atherosclerosis and platelet activation. Prospectively, we examined the effect of cART on the NLR in HIV+ patients presenting to begin cART in Rivers State University Teaching Hospital. *Aim:* This study is aimed at determining the effect of anti-retroviral therapy on Neutrophil Lymphocyte Ratio in Human Immunodeficiency Virus Positive Patients. *Methods:* Four (4) millilitre of blood sample each was collected using a vacutainer containing 0.5 ml of 1.2 mg/ml of K_2EDTA was collected from 40 subjects recruited for the study. Samples were collected at entry into the study, after 3 months and 6 months on ART respectively for Full Blood Count using a 3-part Sysmex XP300 and HIV Viral Load with RT-PCR using Cobas TaqMan version 1.5 (Roche Molecular Systems). *Results*: Subjects mean age was 36.20 years, 14 (35%) of them were males and 26 (65%) were females. Mean Neutrophil: Lymphocyte ratio and HIV viral load (VL) at Month 0, 3 and 6 months were 1.539±1.094 and 215767.85±360338.04 cp/ml, 0.902±0.358 and 705.650±684.220cp/ml and 29.330±17.869cp/ml 0.676±0.171 respectively. There was a statistically significant increase ($p < 0.001$) in the measured parameters. *Conclusion*: There is a plethora of proof which this study agrees with and that is the fact that viral load and inflammation in HIV+ patients reduce considerably by cART. Study has validated the prognostic effect of NLR in the early detection of inflammation. It is therefore necessary to routinely review cART impact using NLR. It is therefore necessary to routinely review cART impact using NLR.

Keywords: Neutrophil/Lymphocyte Ratio (NLR), Combined Antiretroviral Therapy (cART), Human Immunodeficiency Virus (HIV), Viral Load (VL)

1. Introduction

One of the key pathophysiological factors in a disease state is inflammation. In contemporary times, Neutrophil/Lymphocyte Ratio (NLR), Platelet/ Lymphocyte Ratio (PLR) C-reactive protein, serum albumin, erythrocyte sedimentation etc. have been of immense help in routine checks [1] Neutrophil/lymphocyte ratio (NLR) is a newly prognostic tool which act as a marker of inflammation, endothelial damage as well as predictor of mortality in kidney patients and HIV patients [1-3].

1.1. Functional Changes Responsible for This Ratio Neutrophils

Neutrophils, the immature phagocytes with a short half-life, possess the ability to release proteolytic enzymes and oxygen free radicals, viably adding to the unpleasant effects of inflammatory conditions.

Neutrophils relate with the endothelium while in the vessels, where they make proteins available from their granules that

signal the formation of molecular pointers in the bid to assemble and incite other inflammatory cells. Chemotaxis comes into play through the effects of Leukotrienes, which also synergize with the neutrophils. These all play major role in the effect of immunoregulation [4].

Furthermore, neutrophils can form pathogen trappers. Supramolecular complexes are also involved in the atherosclerosis process [5, 6]. When neutrophils are activated, the stabilization of atherosclerotic plaques which is aided by oxygen free radicals and some matrix metalloproteinases is altered [MMP].

Hence, it is imperative to categorically state that when neutrophils are activated, they become essential features in atherogenesis and cardiovascular risk [5, 6].

1.2. Platelets

Platelets, which are cell fragments with nucleus, find their origin from megakaryocytes. Their haemostatic and prothrombotic ability have gained much popularity [7, 8]. Nevertheless, it is only very recently that investigations have been carried out in their proinflammatory ability [7]. Though platelets relate well with various immune cells, their existence with endothelial cells and leucocytes is counted more significant [7, 9, 10].

When atherosclerosis sets in, the anti-adhesion properties of platelets are altered due to inflammation, therefore, platelets relate more with the endothelium. All these will cause numerous inflammatory consequences which is similar to occurrence in thrombosis and haemostasis. Chemostatic effect occurs which induce chemokine in target cells primarily neutrophils and other granulocytes causing their migration to the site of infection and inducing phagocytosis on arrival, due to secretion of cytokines when platelet activation increases [9, 10].

In the involvement with atherogenes, platelets and leucocytes relate well and as such enable cells to assemble at the site of lesion through selectins and integrins [11, 12].

1.3. Lymphocytes

Lymphocytes impacts negatively on atherosclerosis as a result of the effect of Th1 cells and protective from the action of regulatory Th2 and CD4+Foxp3+cells (Tregs) [13, 14]. LDL in its oxidized form, resonate dendritic cells, giving strength to T cells in the control of “pro-atherogenic” line including Th1 or Th17 [13, 15].

The Th2 lymphocytes, correlates with interleukin-19 (IL-19), affecting the anti-inflammatory state which works in support of these pathways: GATA3 and Foxp3 weaken the atherosclerotic activities. The increase in circulating Th2 may be responsible for a lower risk of myocardial infarction [13, 16].

1.4. Inflammation

In the light of everything said above, conclusion should be drawn to the fact that the aforementioned indices are pointers of inflammatory imbalance in which there is a control of effector cells which basically cause the formation of neutrophils and platelets, over regulatory cells such as CD4 cells in particular [17].

The most widely used drug in the treatment of Human Immunodeficiency Virus (HIV) is Antiretroviral Therapy (ART). The combination of these drugs is very useful and successful in fighting the deadly disease. This combination is widely known as combined antiretroviral therapy (cART). cART, invariably cannot remove completely the disease from the body but can limit to the barest minimum, HIV replication. It inevitably means that cART helps in the return of immune function of patients on therapy. An increased neutrophil/lymphocyte ratio (NLR) is linked to a higher risk of cardiovascular disease (CVD) as has been propagated by Abe *et al*. [18], whose research revealed that a higher NLR was linked to high possibility for occurrence of CVD-related issues, which involves both patients who have just begun therapy in no distant time when CVD begins and those on follow up when CVD activities would have started for a long time. To reduce untimely death in HIV + patients, it is highly important to use an accurate risk predictor. NLR is one of such predictors to assess effect of inflammation [19]. The concept of chronic inflammatory and cardiovascular events as it relates with NLR is not widely known. This research, hence, looks at the assessment of the effect of Anti-retroviral Therapy on NLR and coagulation indices, assess if there was any significant relationship between the HIV Viral Load, NLR, coagulation indices and determine if the effect is sustained for up to 6 months into cART.

Neutrophil/Lymphocyte ratios (NLR) among other complementary haematological parameters are used to interpret fluctuations of PLR value as an inflammatory marker, hence increasing the value of PLR. This helps to provide additional information about the disease activity [20].

When predictors of inflammation are high in circulation, to tell the levels of occurrence and mortality for cardiovascular (CV) issues and cases not related to CVD [21-23], the occurrence of these inflammatory markers strongly linked to high possibility of death due to no specific cause particularly among adults [24, 25].

In contemporary times, neutrophil/ lymphocyte ratio (NLR) a derivative of white blood cell component which associates with systemic inflammation and hence is a predictor of morbidity and mortality for both CVD and diseases not related to CVD [26, 27].

No specific cut-off marks have been set for NLR for the purpose of clinical issues, putting into consideration, patient variability during medical check-ups [26, 27]. Numerous chronic situations often give rise to the inflammation [28]. It is a statement of fact that mortality results from cardiovascular diseases (CVDs) worldwide, irrespective of contemporary advancement in medicine. Atherosclerotic process results from inflammation [29].

Conditions relating to inflammation can be examined using the most mundane and less expensive technique such as the use of White blood cell (WBC) count [30]. WBCs and inflammation are in strong affinity especially in CVDs [31].

2. Materials and Methods

2.1. Study Area and Subjects

The study was carried out in Rivers State University Teaching Hospital, Port Harcourt. The geographical location of Rivers State is Latitude 4°31′ - 5°31′ and longitude 6°30′-7°21′. Rivers State University Teaching Hospital, Port Harcourt is a 346-bed specialist hospital owned by Rivers State Government.

2.2. Study Population

The study covered a period of six months during which a total of forty [40] patients presenting for anti-retroviral therapy enrolment, of which 14 and 26 were male and female; age range of 20-45 years were enlisted, attending Rivers State University Teaching Hospital, Port Harcourt, and were strictly followed for their viral load and haematological parameters, within the follow up period which included baseline, three months and six months respectively. The inclusion criteria were only patients newly confirmed as HIV positive, only patients who have not been on ART, only subjects within 20-45 and Patients enrolled into Art clinic after confirmation of HIV status. Exclusion criteria were Patients who have not been confirmed HIV positive, HIV patients not yet exposed to ART but not willing to enrol into ART clinic after confirmation, Patients below 20 years, HIV patients above 45 years and Patients who had commenced ART. Demographic characteristics of study subjects were obtained through questionnaire and before commencement of blood collection, informed consent was obtained from each of them.

2.3. Ethical Consideration

Ethical clearance for study was obtained from the ethical committee of the Rivers State Ministry of Health.

2.4. Blood Sample Collection and Processing

A total amount of 6ml of blood was taken from each patient by venous puncture, 4.0 mL was put into EDTA anticoagulant bottle for viral load testing and 2.0 mL was put into another EDTA bottle for haematological investigations.

2.5. Determination of Viral Load Values Using the cobas® Ampliprep/cobas® taqman® 96 (Real Time PCR)

Procedure

Procedures for Start up were carried out and Loading of reagents into the COBAS® AmpliPrep Instrument. Samples were brought to room temperature after removal from storage. Consumables were loaded on the COBAS® AmpliPrep Instrument. Orders were made and sample racks were loaded into the COBAS® AmpliPrep Instrument. Activation of the start button of the COBAS® AmpliPrep Instrument was made. Results were reviewed and accepted by using the AMPLILINK software.

2.6. Determination of Haematological Parameters by Haematology Auto-analyzer

The haematological parameters investigated include Haematocrit, Haemoglobin, Red Blood Cells, Platelets, White blood cell, Netrophils, MXD (The MXD comprise of Basophils, Eosinophils and Monocytes generated by a three- part automated haematology analyzer). Sysmex Xp-300 Haematology Auto- Analyser, Model NO: XP-300 KOBE Japan.

2.7. Procedure

After allowing samples to mix for 10 minutes in the mixer, the power switch was turned on. Self check, automatically performance of auto-rinsed and background check were made. Introduction of control samples were made into the instrument through the probe. While sample were introduced through the probe with a gentle tap on the start button for easy up take of sample. A double buzzer sound was heard (beep, beep), and analysing was displayed and the immediate removal of the sample. Test result was displayed on the LCD screen.

2.8. Data Analysis

Data was statistically collected and analyzed using calculations of simple percentage and pearson correlation analysis.

3. Results

A total of 40 clients were recruited, with a mean age of 36.20 years, 14 (35%) of them were males. Details are shown in Table 1.

Table 1. *Social Demographic Characteristics of the Study Population.*

Variable	Frequency (n)	Percent (%)
Sex		
Males	14	35.0
Females	26	65.0
Age Group		
≥25	3	7.5
26-35	11	27.5
≤36	26	65.0

Mean Age: 36.20.

Neutrophil/lymphocyte ratio reduced over the study period as shown in Table 2 below.

Table 2. *Neutrophil/Lymphocyte ratio over the period.*

Variable	Mean ±SD	95% C.I. Lower Upper	F-Value	P-Value
Month 0	1.539±1.094	1.189 1.889	17.705	<0.001
Month 3	0.902±0.358	0.788 1.017		
Month 6	0.676±0.171	0.622 0.731		

Comparison of viral load over study period showed significant reduction in viral load values in the sixth month when compared with the third month and month 0, as shown in Table 3.

Table 3. *Comparison of the viral load over the period.*

Variable	Mean	Standard Deviation	95% C.I. Lower Upper	F-Value	P-Value
Viral Load					
Month 0	215767.850	360338.040	100526.15 331009.55	14.293	<0.001
Month 3	705.650	684.220	486.83 924.47		
Month 6	29.330	17.869	23.61 35.04		

4. Discussion

This study shows a statistically significant reduction in Neutrophil/lymphocyte ratio (NLR) over the study period which agrees with that of Raffeti *et al.* [32], whose study revealed NLR values measured at baseline and those measured during follow-up as predictive of death in their study subjects.

The NLR undoubtedly show equilibrium in innate (neutrophils) and adaptive (lymphocytes) immune issues [33-35].

NLR as a prognostic tool plays a vital role in varying ailments, including cardiovascular disease and malignancy, systemic infection or inflammatory disorders [36].

NLR and platelet lymphocyte ratio (PLR) are cheap tools used in the estimation of inflammation [20].

Li *et al.* [13] stressed that raised NLR values are connected to advanced level of an ailment. This strongly agrees with ours, in that, though NLR started with a high value from the baseline as study subjects have not been exposed to cART and had high viral load value. NLR values reduced subsequently over study period. This is predicated upon the fact that cellular demands of these blood components emanate from the endothelial dysfunction as a result of cART intake.

Our study is also in line with that of Osime and Innih [37] whose work showed a significant decrease ($P< 0.05$) in the NLR after giving therapy at varying doses; 15 mg/kg, 20 mg/kg and 25 mg/kg respectively, using laboratory animals. NLR values dropped significantly ($P< 0.05$) as the dose given was raised to 35 mg/kg. This is predicated on the reason that the laboratory animals are familiar with therapy [38].

The research work of Euginia *et al.* [39] which showed that NLR level remained low throughout the follow-up period is as well in line with our study, which showed no appreciation in the value of NLR during follow up period. This will mean that cART is highly beneficial in the reduction of viral load to undetectable levels as well as in tackling issues of inflammation. Reduction seen in NLR has a strong correlation with the positive impact of cART on haematopoiesis. It simply means that cART recovers the haematopoietic stem cells with full restoration of HIV patients. A dependable prognostic tool with high accessible feature aimed at reducing high morbidity and mortality is very critical in salvaging HIV patients.

Finally, comparison of viral load over study period showed that viral load significantly reduced in the sixth month when compared with the third month and at month 0. This is in agreement with studies carried out by Moore-Igwe *et al.* [40], whose study subjects achieved 100% viral suppression rate. In other to achieve viral suppression, HIV+ patients should take their treatment religiously as prescribed.

The study has shown that viral suppression correlates positively with NLR. This implies that when viral load is high, the value of NLR becomes high. However, when cART is commenced, viral load level drops alongside the predictor of inflammation (NLR). Worthy of note is the fact that the effect of cART on NLR is sustainable for up to 6 months, seeing that the persistent low levels of inflammation throughout follow –up period was maintained.

All these could be due to the strong impact of cART on neutrophil and lymphocyte producing cells (multipotent cells) in the bone marrow by altering their normal function. However, the bone marrow seems to normalize as the body begins to get used to the therapy.

5. Conclusion

There is a plethora of proof which this study agrees with and that is the fact that viral load and inflammation in HIV+ patients reduce considerably by cART. However, inflammation is not completely eradicated and this is why it can lead to persistent inflammatory conditions, morbidity and mortality amongst this category of patients. It is therefore necessary to routinely review cART impact using NLR. The identification of high-risk subjects presenting varying health issues is enabled with the use of NLR, a prognostic tool which makes it easy to monitor patient's medical output. Since NLR display high levels when disease is in advanced state and low levels during follow – up. It is therefore imperative to include NLR in monitoring patients progress with therapy.

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