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Role of Absolute Reticulocyte Count in Evaluation of Pancytopenia in Patients Undergoing Bone Marrow Biopsy

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ABSTRACT

Background: Pancytopenia is a hematological condition characterized by a simultaneous decrease in red blood cells, white blood cells, and platelets, reflecting a wide spectrum of underlying bone marrow pathologies. Bone marrow biopsy remains the gold standard for diagnosis; however, in this context, the absolute reticulocyte count (ARC) serves as a potentially valuable, non-invasive biomarker reflecting marrow activity and erythropoietic function. **Aims & Objectives:** The primary objectives of this study were to assess the diagnostic utility of ARC in patients undergoing bone marrow biopsy for pancytopenia, to determine whether ARC can accurately predict the underlying etiology, to achieve at least an 80% diagnostic concordance between ARC and bone marrow biopsy results, and to evaluate the feasibility of implementing ARC as a first-line, non-invasive diagnostic approach prior to bone marrow examination. **Methodology:** This comparative cross-sectional study was conducted at the Central Diagnostic Laboratory, Mayo Hospital/King Edward Medical University, Lahore, over a period of 15–30 days following ethical approval. Non-probability convenience sampling was employed to recruit patients fulfilling the diagnostic criteria for pancytopenia. Two milliliters of EDTA-anticoagulated blood were collected from each patient after obtaining informed consent. Samples that were clotted, hemolyzed, lipemic, or insufficient were excluded. The ARC was calculated using the reticulocyte percentage and red blood cell (RBC) count. Data were analyzed using SPSS version 23, with quantitative variables expressed as mean ± standard deviation (SD) and qualitative variables presented as frequencies and percentages. **Results and Findings:** A total of 147 pancytopenic cases were analyzed. The most prevalent underlying cause was aplastic anemia (n=61; 41.4%), followed by leukemia (n=40; 27.2%), myelodysplastic syndrome (MDS) (n=17; 11.6%), infections (n=14; 9.5%), megaloblastic anemia (n=11; 7.5%), and bone marrow necrosis (n=4; 2.7%). The mean ARC was lowest in aplastic anemia and necrosis (11.7×10^9/L and 3.9×10^9/L, respectively), indicating markedly reduced marrow activity. Megaloblastic anemia (18.36×10^9/L) and MDS (26.1×10^9/L) demonstrated moderately low values, while infections (105.9×10^9/L) and leukemia (81.06×10^9/L) showed significantly elevated ARC levels, suggesting hyperactive marrow response. A strong correlation was observed between ARC levels and bone marrow biopsy findings, supporting ARC's role as a predictive diagnostic parameter. **Conclusion:** The study demonstrates that the absolute reticulocyte count is a reliable, non-invasive, and rapid indicator of bone marrow activity, showing a strong diagnostic correlation with bone marrow biopsy findings in pancytopenia. ARC can serve as an effective preliminary tool for differentiating hypo-productive and hyper-productive marrow conditions such as aplastic anemia, megaloblastic anemia, leukemia, and infections. While bone marrow biopsy remains indispensable for definitive diagnosis and prognosis, incorporating ARC as an initial diagnostic measure could enhance clinical decision-making and reduce unnecessary invasive procedures.

INTRODUCTION

Pancytopenia is a condition presented in haematology laboratory on the assessment of CBC (Complete Blood Count). (1) In this condition the CBC reports of patients show a significant decrease in all blood cell indices below their reference ranges. The presenting symptoms are often

characterized as anaemia, leucopoenia and thrombocytopenia. Pancytopenia is not a disease. It is merely a clinical presentation with some underlying cause. (2, 3) The threshold to detect pancytopenia is that the patient should present with haemoglobin (Hb) less than 13.5g/dl in men or 11.5g/dl in women; the leucocytes to be counted is much less than 4x103/L and the platelets count is much less than 100x103/L. (4) Causes of pancytopenia can be numerous depending upon epidemiological factors. Pancytopenia presents in males usually in higher ratio than females. Pancytopenia shows a male to female ratio of 2:1. (5) The mean age range for the presentation of pancytopenia is 10-30 years for an age group of 1-79 year. (6) After the clinical demonstration of pancytopenia in the complete blood count of the patient, there is a need for the diagnosis of the underlying cause. (7) Pancytopenia can be caused as a result of marrow suppression, reduced hematopoietic cell production and reduced cellular differentiation. The most common cause of pancytopenia is Megaloblastic anaemia (28.64%), followed by infection (27.56%), aplastic anaemia (20.54%), leukaemia (11.35%), mixed deficiency anaemia (4.32%), visceral leishmaniasis (3.78%), metastasis (2.7%) and Myelodysplastic syndrome (1.08%). (1) It is necessary to evaluate the pathology of pancytopenia because its severity is suggestive of management and prognosis. (8) And, as a result it will assist in therapy. Usually bone marrow aspiration and biopsy is indicated and considered important where the underlying cause is not identified. (9) Even though acute leukaemia and bone marrow failure syndromes are traditional reasons of pancytopenia, etiologist which include infections and megaloblastic anaemia also make contributions. Bone marrow is suggestive of the pathology of pancytopenia but it is an invasive procedure. It is usually suggested if the non-invasive procedures like CBC, vitb-12, Serum foliate, Serum Iron, are not conclusive of the underlying cause of pancytopenia. (1)

Absolute retic count is defined as the amount of reticulocyte present in per micro-litre of blood ranging normally from 50-100x109/L per litre of blood. Absolute Retic Count usually determines red cell production in haemopoiesis. For the preliminary diagnosis of pancytopenia ARC is a helpful marker. It plays a pivotal role in patients undergoing bone marrow biopsy by differentiating the underlying pathologies of pancytopenia. It is suggestive of hyper proliferative and hypo proliferative anaemia. (10) It is a calculated figure as it cannot be directly measured. For the calculation of ARC, we use two parameters namely; blood retic percentage and RBC count. (11)

It is calculated by the formula;

ABSOLUTE RETIC COUNT = [RETIC (%age) x RBC (x1012/L)]/ 100

Normal value for reticulocyte percentage is 0.5-2.0% and for ARC it is 50-100x109/L. (10, 12)

This study is designed to calculate the ARC of patients undergoing invasive procedures like bone marrow biopsy to evaluate the underlying cause of pancytopenia, benefiting the patient for further management. Thus, expensive tests and invasive procedures can be avoided. Majorly presented as a result of Megaloblastic anaemia, aplastic anaemia and certain leukaemia; pancytopenia is presented in hospitals which requires bone marrow biopsy. For the evaluation and diagnosis of results many hospitals use the algorithm approach. According to this approach, after the clinical assessment of patient, patent undergoes a series of non-invasive procedures, fore mentioned Serum b-12. Serum folate etc. Many any parameters like, RDW, MCV, HCT are also correlated with the diagnosis. The main Objective of this study is to evaluate the importance of absolute reticulocyte count for patients undergoing bone marrow biopsy and correlation with underlying causes.

Operational Definitions

- ***Pancytopenia:*** A haematological condition presented in hospitals, which upon laboratory diagnosis shows a decrease in all blood cell counts. It shows Hb to be less than 13g/dl in males and 11.5 in females, and TLC less than 4,000 per micro-litre and Platelets less than 100,000 per micro-litre of blood. (13)
- ***Absolute Retic Count:*** Absolute retic count is defined as the amount of reticulocyte present in per micro-litre of blood ranging normally from 50- 100x109 per litre of blood. (14)

Hypothesis

H₁. *Absolute retic count is lower than normal in Aplastic anaemia and necrosis.*

H₂. *Absolute retic count is moderately low in Megaloblastic anaemia/mixed anaemia/Myelodysplastic anaemia*

H₃. *Absolute retic count is higher in infection and leukaemia.*

MATERIAL AND METHODS

The study design was approved by the Institutional Review Board. Before the start of research, a pre-research planning was done in which all the aspects were considered. It included selection of research site, target population, sample size, self-designed Performa, sampling method, research methodology, organizational issues and work plan. Logistics and ethical implications were thoroughly discussed with the supervisor at Department of Pathology, King Edward Medical University Lahore. This is a Comparative, cross-sectional study. Study was conducted in haematology department of KEMU. Study duration was 15-30 days after approval of synopsis. This study was conducted from 25th April, 2020 to 20th February, 2021. Sample size is 147 patients presented at Haematology Department in Mayo Hospital Lahore. Non-Probable convenient sampling technique was used. Sample size of 182 patients, (1 patient each group is estimated using 5% level of significance, 90% power of test, with expected percentage megaloblastic anaemia as 28.6% and leukaemia as 11.35%. Following equation was used.

$$N = \left(\left(z(1-\alpha) \times \sqrt{2 \times \bar{P} \times (1 - \bar{P})} + z(1-\beta) \times \sqrt{P1 \times (1 - P1) + P2 \times (1 - P2)} \right)^2 \right) \div (P1 - P2)^2$$

For sample selection inclusion criteria and exclusion criteria was used. As for Inclusion Criteria; all the samples received at Mayo hospital, Lahore, approving the criteria

of pancytopenia. i.e., Hb. < 13g/dl in males and 11.5 in females, TLC <4,000/ul and Platelets <100,000/ul. On contrary, all samples not meeting the criteria of pancytopenia, all the samples not having 2ml volume of whole blood in EDTA vial, spurious Results, haemolysed Sample, patients on drugs affecting pancytopenia, patients with incomplete information will be excluded.

After informed consent relevant information of subjects like age, gender, body weight and results of healthy subjects were noted on Performa. (Appendix 1). Under aseptic measures 2ml EDTA blood sample was drawn from the study subjects with subject ID. After the collection of whole blood, samples were analysed in the Haematology section of Mayo Hospital using complete blood counter SYSMEX XN-1000. Peripheral smears were stained by Geimsa, reticulocyte stain and examined under microscope for confirmation of platelet count, morphology, reticulocyte percentage. Upon presentation of the symptoms like, pallor, icterus, lymphadenopathy, hepatosplenomegaly and sternal tenderness, patients did undergo a procedure of bone marrow biopsy. The peripheral blood smear was also being examined. The result of each sample was noted on Performa. Calculated results of ARC and results of bone marrow biopsy were correlated and recorded accordingly. ARC was calculated using the formula:

ABSOLUTE RETIC COUNT = [RETIC (%age) x RBC ($x10^{12}$/L)] /100

For Statistical Analysis all collected data was entered and analysed by using Statistical package for social sciences (SPSS version 23). Quantitative variables like age, gender was presented as mean ± SD. Qualitative variables like gender was presented as frequency and percentage.

RESULTS

The study was carried out over the period of three months. A descriptive cross-sectional study was carried on 147 pancytopenia patients with a mean Hb (g/dl)7.05±2.05, Mean TLC(x103/L) 2.8±1.17 and Platelets(x109/L) 44.1±33.7.

Table 1

Number of Groups with underlying causes

Groups	Causes	Mean± SD
group-1	Aplastic Anaemia	61cases (41.5%)
group-2	Leukaemia	40cases (27.2%)
group-3	Megaloblastic Anaemia	11cases (7.5%)
group4	Infection	14cases (9.5%)
group-5	Myelodysplastic syndrome	17cases (11.6%)
group 6	Necrosis	4cases (2.7%)

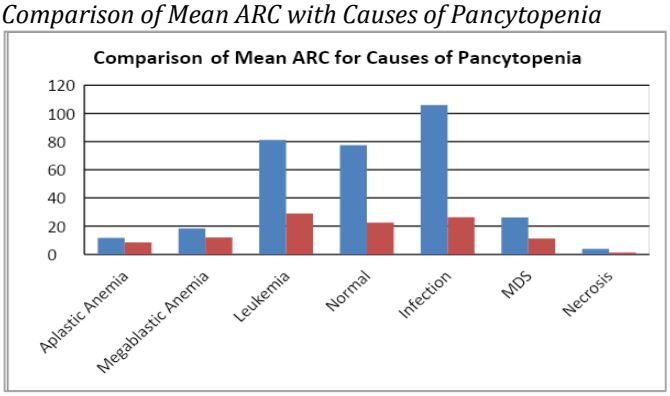
Table 2

Haematological parameters Retic and ARC correlation with causes of pancytopenia

Causes	Mean Age	Mean RBC ($x10^{12}$/L)	Mean Hb (g/dl)	Mean TLC ($x10^3$/L)	Mean platelet ($x10^9$/L)	Mean Retic count	Mean ARC (x109/L)
Aplastic Anaemia	30±12	2.57±0.89	5.9±1.8	2.6±1.02	31.7±16.9	0.5	11.7±8.5
Megaloblastic Anaemia	32±14	3.3±0.6	7.78±1.9	2.5±0.6	30.81±24.6	0.5	18.36±12.05
Leukaemia	29±1.3	3.45±0.9	7.64±0.13	3.2±1.4	46.1±44.4	2.2	81.06±28.94
Infection	12±5.8	3.4±0.51	8.1±1.4	3.0±0.6	71.5±30.8	3.0	105.9±26.29
MDS	31±18.5	3.1±0.94	7.6±2.5	2.6±1.33	67.7±33	0.8	26.1±11.24
Necrosis	23±13	3.9±1.3	9.9±1.4	3.1±1.5	54.5±32.2	0.1	3.9±1.3

Figure 1

Comparison of Mean ARC with Causes of Pancytopenia



Based on clinical history and laboratory tests undergoing for bone marrow aspiration and biopsy, there were 99(67.3%) male and 48(32.7%) female in all groups. Mean age in group 1 (Aplastic anaemia) was 30±12, group 2 (leukaemia) was 29 ±1.3, group 3 (Megaloblastic anaemia) was 32±14, group 4 (infection) was 12.1±5.8, group 5 (MDS) was 31±18.5 and group 6 (necrosis) was 23±13.57. All causes of pancytopenia showed significant difference in their ARC values. In patients with diagnosis of Aplastic anaemia, necrosis, the absolute retic count was 11.7x109/L and 3.9x109/L respectively. For Megaloblastic anaemia and MDS Absolute retic count was 18.36x109/Land 26.1x 109/L. And, for infection and leukaemia ARC is 105.9x109/L and 81.06 x109/L. Value of p was found by using Pearson correlation by comparing two quantitative groups of diagnosis and values of ARC. The value of p is less than equal to 0.05.

DISCUSSION

The patients included in this study had pancytopenia and presented for workup. The confirmation of pancytopenia was made on peripheral blood smear (PBS) and absolute retic count (ARC) was calculated. Diagnosis for aetiology of pancytopenia was made on examination of bone marrow aspiration and biopsy; and correlated with ARC value. (6) We divided all cases on the basis of diagnosis. These group are labelled as Group 1(Aplastic anaemia), group 2(Leukaemia), group 3 (Megaloblastic anaemia) group 4 (Infections) group 5 (MDS) and group 6 (Necrosis). Although bone marrow aspiration biopsy an invasive procedure and is not required in Megaloblastic anaemia, but this is performed on clinicians demand. The most common cause of pancytopenia in our study is Group-1(Aplastic anaemia) with a frequency of 60 cases and percentage 41.5%. Group 2(Leukaemia) is second most common cause is our study40 cases (22.9%). Muneer

et al shows that aplastic anaemia is the commonest cause of pancytopenia in their study with a prevalence of 38.6% of aplastic anaemia with a total of 130 cases. (15) In contrary Maria et al show that Megaloblastic anaemia is most common cause of pancytopenia. (1) Results of Male to female ratio showed male pre-dominance. The ratio of male to female is 2:1(67.3% male and 32.7% female). Out of total 147 cases, 99 were male and 48 were female. These results are in correspondence to a recent study held in (Dept. of Pathology) Shah Medical Institute, Gujarat, India by RachitSaxena et al. The study showed Male predominance with 64.2% male and 35.7% female. (16) Our study showed mean age in all groups was 28±14. This is similar to a study conducted by Thaker et al at department of pathology GMC Jammu over a period of 2 years showed mean age of 29.48 years including all causes. (17) All causes of pancytopenia shoed mean Hb (g/dl) of 7.05±2.05, Mean TLC(x103/L) 2.8±1.17 and mean Platelets(x109/L) 44.1±33.7. This fulfilled the criteria for Pancytopenia according to guidelines. (18) The diagnosis of underlying cause is usually based on bone marrow aspiration examination. But, ARC plays an important role for the evaluation and preliminary identification of the underlying causes of pancytopenia and it is non-invasive calculated by red cell count and Retic percentage. As Bone marrow is an invasive procedure.

The results of this our study showed that the mean ARC was 11.7x109/L and 3.9x109/L respectively which is lower than 25 for Group-1(Aplastic anaemia) and Group-6(Necrosis) respectively. Group 3(megaloblastic anaemia) and Group-5 (MDS) showed moderately low values of mean ARC 18.36x109/L, 26.1x109/L respectively. Group-2(leukaemia) and Group-4 (infection) show relatively higher values of ARC with an average of 105.9x109/L and 81.06x109/L. It was clinically significant measured by Pearson correlation p-value (0.007) which is less than 0.05. Priya et al showed in their study that ARC is less than 25x109/L in cases of Aplastic Anaemia, and more than 25 to 50x109/L for nutritional anaemias and greater than 50x109/L for marrow infiltration and sepsis. It is similar to our study. (3) Shaikh et al showed similar results like our study their study. The calculated Mean ARC was less than 25x109/L for Aplastic anaemia, 25-50 x109/L for MDS, 50-75 x109/L for Megaloblastic anaemia, 76-100 x109/L for leukaemia, 101-126 x109/L for infection and 126-150 x109/L for leishmaniasis and metastasis. Results of these studies are supporting result of our study held. The values of ARC are significant for the preliminary diagnosis of the underlying cause of pancytopenia. (1) Haematological profile is important to evaluate the diagnosis along with bone marrow aspiration and biopsy. But, further investigation for staging, prognosis of causes of pancytopenia is required. The only limitation of this study was that this study was carried out on small sample size. Further it is recommended that for patients being clinically presented with pancytopenia should be tested preliminarily by ARC before undergoing invasive procedures as Bone marrow biopsy.

CONCLUSION

Both bone marrow Biopsy and ARC are useful in the diagnosis of underlying cause of pancytopenia with ARC being non-invasive procedure. ARC can help in the preliminary diagnosis of underlying cause of pancytopenia as all causes show significant difference in their values.

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