Section: Pathology

Original Research Article

IMPORTANCE OF ABSOLUTE RETICULOCYTE COUNT IN EVALUATION OF PANCYTOPENIA: AN EXPERIENCE OF A TERTIARY CARE CENTER IN EASTERN INDIA

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Received : 28/03/2025
Received in revised form : 18/05/2025
Accepted : 04/06/2025

Keywords:
Pancytopenia, reticulocyte, absolute reticulocyte count, megaloblastic anemia.

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DOI: 10.47009/jamp.2025.7.3.193

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (3); 997-1001

ABSTRACT

Background: Pancytopenia is a prevalent hematological disorder that is frequently encountered in clinical settings. It refers to a decrease in the three major blood cell lines, including red blood cells, white blood cells, and platelets. The absolute reticulocyte count (ARC) is a crucial indicator in detection of underlying cause of pancytopenia, which is critical for accurate diagnosis and management. ARC aids in distinguishing between hypo-proliferative and hyper-proliferative anemia, making it an essential diagnostic tool. **Materials and Methods:** A prospective study was conducted during the period of July 2019 to June 2021 at the Pathology department, MGM Medical College & LSK Hospital, Kishanganj, to evaluate hematological parameters, absolute reticulocyte count, and bone marrow aspiration examination in 220 patients presenting with pancytopenia. The study aimed to investigate the significance of absolute reticulocyte count in the early diagnosis of pancytopenia. **Result:** A total of 220 patients were assessed for pancytopenia in the study, with ages varying from 5 to 80 years and a mean age of 41 years. There was a male predominance among the patients. The absolute reticulocyte count (ARC) was found to be less than 25x109/L for cases of aplastic anemia, between 25-50x109/L for megaloblastic anemia, mixed nutritional deficiency anemia, and myelodysplastic syndrome, and greater than 100x109/L in cases of visceral leishmaniasis, malaria, sepsis, and marrow infiltrative disorders. **Conclusion:** Absolute reticulocyte count (ARC) can play an important role in the early diagnosis of pancytopenia and provide valuable information that may help prevent the need for more invasive and costly investigations.

INTRODUCTION

Pancytopenia is a common hematological disorder characterized by a reduction in the normal range of all three blood cell lines i.e., RBC, WBC, and platelets.[1] This condition may be caused by various diseases that influences the bone marrow's production of these cells, resulting in the concurrent presence of anemia, leukocytopenia, and thrombocytopenia.[2-7] Pancytopenia is not a disease in itself, but rather a combination of three clinical findings that can arise from different conditions that affect the bone marrow, either directly or indirectly.[8-10] Many conditions may manifest as pancytopenia due to decreased production of hematopoietic cells, reduced bone marrow growth, cell differentiation suppression, abnormal cell infiltration, or defects in the production of cells that are eliminated from circulation.[11,12] Bone marrow aspiration is recognized as the gold standard for evaluating cases of pancytopenia,[13-16] and it is recommended for patients with unknown etiology.[17] However, the investigation is an invasive one, painful for the patient and somewhat expensive.

Absolute reticulocyte count (ARC) is a simple and cost-effective test. Also, since the absolute reticulocyte count (ARC) is a measure of red cell production and can distinguish between hypo- and

hyper-proliferative anemia, it can be a helpful marker for the initial assessment of pancytopenia.[11] The ARC is a calculated parameter obtained by multiplying the reticulocyte count percentage by the RBC count.[13] Normal ranges for reticulocyte count and absolute reticulocyte count are ranging from 0.5-2.5% and 50-100X109/L, respectively.[18-20]

This study, therefore, aims to evaluate the importance of ARC in assessment of patients presenting with pancytopenia.

MATERIALS AND METHODS

A prospective study was conducted at the Department of Pathology, MGM Medical College and LSK Hospital, Kishanganj, Bihar, over a period of two years from July 2019 to June 2021. A total of 220 patients were selected for the study based on inclusion criteria that included patients with pancytopenia and aged between 5 and 80 years, with hemoglobin <9g/dl, white blood cell count <4000/µL, and platelet count <1,00,000/µL.[10,13,18,19] Patients undergoing chemotherapy or radiotherapy, those who had received recent blood transfusions, and those outside the age range were excluded from the study. A 3 ml blood were collected from all patients in EDTA vials, and complete blood count and reticulocyte count were evaluated. Absolute reticulocyte count was computed using the formula ARC (thousand/µL) = Reticulocyte % X RBC count (million/µL) X 10).[13] Complete hemogram, peripheral blood smear, and absolute reticulocyte count were used to compare investigation reports to reach a diagnosis.

Statistical analysis: The data was collected and compiled using Microsoft Excel 2007, and statistical analysis was carried out using IBM SPSS Version 21. Mean and standard deviation values were computed for the hematological parameters in all cases.

RESULTS

[Figure 1] illustrates the diagnostic spectrum among the 220 consecutive pancytopenic patients (mean age 41 ± 17 years; male-to-female ratio 1.15:1, [Table 1]). Megaloblastic anaemia was the leading cause (n = 73, 33 %), followed by mixed nutritional-deficiency anaemia (n = 55, 25 %) and aplastic anaemia (n = 40, 18 %). Infective aetiologies (sepsis, malaria, visceral leishmaniasis) and marrow-infiltrative disorders (leukaemia, metastasis, myeloma, myelodysplastic syndrome) together accounted for the remaining 24 % of cases.

Baseline haematological indices for each diagnostic category are summarised in [Table 2] and visualised for red-cell counts in Figure 2. Aplastic-anaemia patients exhibited the most profound cytopenias, with mean haemoglobin 4.7 g/dL, RBC 2.0 × 10^6/µL and platelets 40 × 10^9/L. By contrast, sepsis-associated pancytopenia showed relatively preserved counts (Hb 7.4 g/dL; WBC 3.6 × 10^3/µL; platelets 86 × 10^9/L), reflecting peripheral consumption rather than marrow failure.

Reticulocyte kinetics discriminated sharply between hypoproliferative and hyperproliferative states [Table 3, Figure 3&4]. Hypocellular marrow disorders displayed markedly depressed absolute reticulocyte counts (ARC): aplastic anaemia, 22.5 ± 7.5 × 10^9/L; megaloblastic anaemia, 37.4 ± 12.0 × 10^9/L; mixed nutritional anaemia, 36.9 ± 13.1 × 10^9/L. In contrast, marrow-infiltrative and infective conditions generated robust reticulocytosis, with ARC exceeding 100 × 10^9/L in leukaemia (102 × 10^9/L), sepsis (130 × 10^9/L), malaria (140 × 10^9/L) and visceral leishmaniasis (158 × 10^9/L). Reticulocyte percentages mirrored this pattern, remaining static at ~0.1 % in hypoproliferative anaemias but rising to 3-5 % in hyperproliferative states.

Collectively, these data demonstrate that ARC thresholds of <25 × 10^9/L, 25-50 × 10^9/L and >100 × 10^9/L reliably segregate aplastic anaemia, nutritional/megaloblastic anaemia and marrow-infiltrative or infective pancytopenia respectively. Thus, routine ARC estimation, in conjunction with basic haemogram parameters, provides a rapid, inexpensive triage tool that can guide the need for bone-marrow examination and targeted biochemical assays in patients presenting with pancytopenia.

Table 1: Proportion of cases based on Gender

Gender	Proportions
Male	118 (53.64%)
Female	102 (46.36%)

Table 2: Baseline characteristics of pancytopenic cases in our study (n=220).

Causes	No of cases	Mean Hemoglobin (g/dL)	95% Confidence interval	Mean RBC Count (millions/µL)	95% Confidence interval	Mean WBC Count (x103/L)	95% Confidence interval	Mean Platelets (x109/L)	95% Confidence interval
Megaloblastic anemia	73	7.1 ± 2.1	6.6-7.6	3.1 ± 0.7	2.9-3.2	2.4 ± 0.6	2.2-2.5	60.3±19.8	55.6-64.9
Aplastic anemia	40	4.7 ± 1.3	4.2-5.1	2.0 ± 0.5	1.9-2.2	1.5 ± 0.7	1.3-1.8	39.8±18.4	33.9-45.7
Mixed nutritional	55	6.8 ± 2.2	6.2-7.5	3.0 ± 0.9	2.7-3.2	3.3 ± 0.6	3.1-3.4	76.7±14.2	72.8-80.5

ISSN (O): 2687-5365; ISSN (P): 2753-6556

deficiency anemia									
Sepsis	25	7.4 ± 1.5	6.8-8.0	3.4 ± 0.6	3.1-3.9	3.6 ± 0.3	3.5-3.7	85.9±7.5	82.8-89.0
Leukemia	11	7.3 ± 1.6	6.2-8.3	3.5 ± 0.5	3.1-3.9	2.7 ± 0.7	2.3-3.2	47.5±13.0	38.7-56.3
Metastasis	04	7.8 ± 0.7	6.5-9.0	3.7 ± 0.4	2.6-4.1	3.7 ± 0.1	3.4-3.9	65.0±13.9	42.7-87.2
Myelodysplastic syndrome	03	7.6 ± 0.8	5.5-9.8	3.2 ± 0.5	1.8-4.5	3.7 ± 0.1	3.3-4.1	79.3±10.5	53.0-105.6
Malaria	03	7.5 ± 0.6	6.0-8.9	3.7 ± 0.3	3.0-4.5	3.5 ± 0.5	2.1-4.8	61.6±10.1	36.7-86.5
Visceral leishmaniasis	04	8.3 ± 0.8	6.9-9.7	3.9 ± 0.2	3.5-4.2	3.3 ± 0.8	2.0-4.5	88.0±5.5	79.0-96.9
Multiple myeloma	02	7.5 ± 0.4	3.6-11.3	3.5 ± 0.1	2.2-4.7	3.5 ± 0.3	0.3-6.7	62.5±3.5	30.7-94.2

Table 3: Descriptive statistics of reticulocyte percentage & Absolute Reticulocyte Count

Cause	Reticulocyte Count (%)	Confidence interval (95%)	Absolute Reticulocyte Count (x109/L)	Confidence interval (95%)
Megaloblastic anemia	0.1 ±.07	0.12-0.15	37.4±12.0	34.6-40.2
Aplastic anemia	0.1±.02	0.09-0.11	22.5±7.5	20.1-24.9
Mixed nutritional deficiency anemia	0.1±.02	0.11-0.14	36.9±13.1	33.4-40.5
Sepsis	3.7±.91	3.4-4.1	129.6±40.7	112.8-146.5
Leukemia	2.7±0.5	2.3-3.1	102.1±36.8	77.3-126.9
Metastasis	4.4±0.4	3.6-5.1	111.5±47.9	35.2-187.2
Myelodysplastic syndrome	0.1± .00	.00 - .00	94.8±171.4	171.4-361.0
Malaria	5.2 ±0.3	4.3-6.1	139.7±101.0	112.6-390.6
Visceral leishmaniasis	0.4±0.1	0.2-0.7	157.7±41.6	91.4-224.0
Multiple myeloma	2.3± 2.6	21.8-26.4	141.5±1.82	125.1-157.9

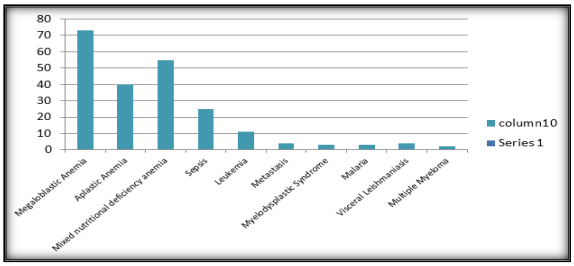

Figure 1: Number of cases according to their diagnosis

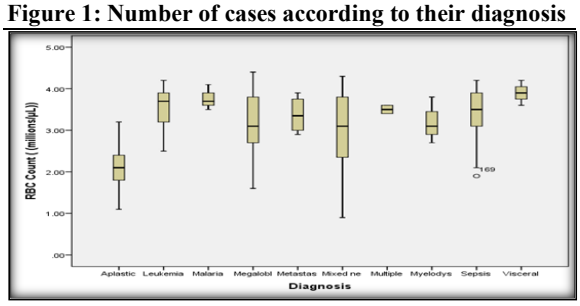

Figure 2: Box whisker plot depicting the comparison of median and inter quartile range of RBC count regarding the causes of pancytopenia studied.

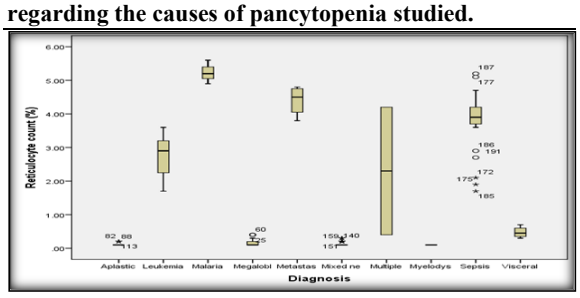

Figure 3: Box whisker plot depicting the comparison of median and inter quartile range of reticulocyte count in percentage (%) regarding the causes of pancytopenia studied.

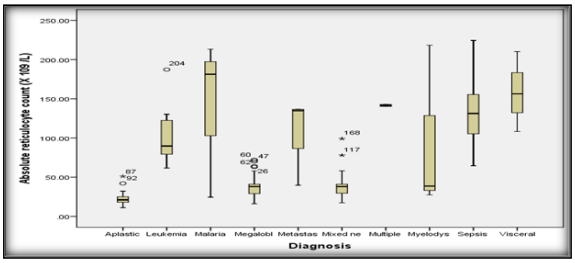

Figure 4: Box whisker plot showing the relationship of median and inter quartile range of absolute reticulocyte count regarding the causes of pancytopenia studied.

DISCUSSION

The study showed a male preponderance among the patients, like the study carried out by Garg AK et al,[1] Patel G R et al,[3] BN Gayatri et al,[10] Poorana Priya P et al,[13] Knodke K et al,[15] Khunger et al,[22] Das J et al,[24] and Niazi M, et al.[25] While few study like Jain A et al,[5] and Jiskani SA et al,[11] showed female preponderance in their study. Among various factors responsible for pancytopenia, megaloblastic anemia was found to be the commonest one, which is similar to other studies.[3,5,7,11,13,15, 22-24] We found various causes of pancytopenia in our study such as megaloblastic anemia (33.18%), aplastic anemia (18.18%), mixed deficiency anemia (25%), leukemia (5%), sepsis (11.36%), visceral leishmaniasis (1.81%), metastasis (1.81%), Malaria (1.36%), multiple myeloma (0.90%) and myelodysplastic syndrome (1.81%). Gayathri et al,[10] in her study showed that the commonest cause of pancytopenia was megaloblastic anemia (74.04%) which was

ISSN (O): 2687-5365; ISSN (P): 2753-6556

followed by aplastic anemia (18.26%) whereas Sindhu et al,[26] found that aplastic anemia (33.7%) was most common cause of pancytopenia and succeeded by megaloblastic anemia (32.55%). Jha A et al,[16] showed in his study that hypoplastic anemia was the most common factor behind pancytopenia. On the other hand Keisu M et al,[27] showed neoplastic diseases and radiation to be the most common etiologies of pancytopenia while Bae MH et al,[28] found acute myeloid leukemia (AML) to be the most common cause of pancytopenia in there study. Vargas-Carretero CJ et al,[29] showed myelodysplastic syndrome (MDS) was the most common cause of pancytopenia, followed by megaloblastic anemia.

In our study, we found that the absolute reticulocyte count was a significant factor. We observed a significant difference in the absolute reticulocyte count among various causes of pancytopenia. Aplastic anemia had a count of less than 25 x109/L, Megaloblastic anemia and Mixed nutritional deficiency anemia had a count of 25–50 x109/L, Myelodysplastic syndrome had a count of 51–100x109/L, and leukemia, sepsis, malaria, metastasis, multiple myeloma had a count of 101–150x109/L, while Visceral leishmaniasis had a count of 150–160x109/L [Table 3]. These results are consistent with the findings of Jiskani SA et al and Priya et al,[11,13] which reported that the ARC was <25x109/L in aplastic anemia, 25–50x109/L for nutritional anemia, and >100x109/L in bone marrow infiltration and sepsis.[19]

The absolute reticulocyte count (ARC) is an important indicator of red blood cell production in the bone marrow. It plays a critical role in determining the underlying cause of pancytopenia and in distinguishing between hypoproliferative and hyperproliferative anemia. This has been noted in previous studies, such as Jiskani et al.[11]

In cases of pancytopenia with ARC less than 25,000/µL, bone marrow aspiration is necessary to rule out aplastic anemia. For cases with ARC more than 100,000/µL, bone marrow aspiration is again recommended unless there is a suggestive history of sepsis or malaria. Pancytopenia with ARC ranging from 25,000 to 50,000/µL should undergo serum B12, folate, and ferritin assays first.[13] If one of these is parameters found to be low, then bone marrow aspiration is unnecessary. Our study revealed that every specific cause of pancytopenia exhibits a difference in ARC, which may aid in the initial diagnosis of pancytopenia before resorting to an invasive procedure, such as bone marrow examination. Nevertheless, a complete hematological workup with clinical correlation is essential in investigating the underlying processes of pancytopenia.[10,11,30]

CONCLUSION

Determining the underlying cause of pancytopenia is crucial, and the absolute reticulocyte count (ARC) is a valuable indicator in this regard, along with the peripheral blood smear. Our study suggests that ARC is a better diagnostic tool than routine reticulocyte count, especially in differentiating aplastic anemia from hypoproliferative anemia. Additionally, in cases of mixed nutritional anemia, it is recommended to evaluate other parameter like serum B12, folate, and ferritin levels. Adopting a systematic approach to the diagnosis of pancytopenia may avoid unnecessary invasive procedures, such as bone marrow aspiration.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556