

Abnormalities of Hemoglobin Levels in Acute Myeloid Leukemia Patients : A Systematic Review

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Abstract

Introduction: Acute Myeloid Leukemia is the common type of leukemia in adults, with an incidence of 20,000 per year in the US. The proliferation of white blood cells can affect other blood cells. Red blood cells are important in transporting oxygen to body tissues. Disruptions in the production of red blood cells can impact the clinical condition experienced by patients. Hemoglobin levels can decrease when there are disruptions in red blood cell production. **Methods:** This systematic review is aiming to know the abnormalities in hemoglobin levels in AML patients. The PRISMA flow diagram was used to select the literature to be reviewed. The study was conducted on a population of patients diagnosed with AML using an observational research design. AML patients with secondary diseases and those who had undergone therapy were excluded. A total of three literature meeting the inclusion and exclusion criteria were selected for review in this study. The quality of the literature was then assessed using the JBI critical appraisal tools to minimize the risk of bias. Literature search was done using Pubmed, DOAJ, and ScienceDirect, with 'Acute Leukemia', 'Acute Myeloid Leukemia', 'Hematological Parameters', and 'Hemoglobin' as the keywords. **Results:** A total of three literature were obtained and analyzed. These three studies shows outcomes with low hemoglobin levels. The results obtained by Suchismita et al., 2023, indicate an average hemoglobin value of 7.2 ± 2.0 g/dL. Sanchez et al., 2015, reported a median hemoglobin value of 7.7 (5.6-12.5) g/dL. Meanwhile, Merdin et al., 2020, reported a median hemoglobin value of 8.9 g/dL. **Conclusion:** This systematic review shows that AML patients has a lower levels of hemoglobin than normal, with moderate to severe anemia. Further research is needed to identify the risk factors causing low hemoglobin levels in AML patients.

Keywords : Acute Myeloid Leukemia; Hemoglobin

1. Introduction

Leukemia is a term used for a cancer that affects the bone marrow, causing the body to produce more white blood cells than normal, which disrupts the body's ability to fight infections. Leukemia becomes dangerous because the excessive number of white blood cells can disturb the production of other blood cells. In America, leukemia is among the top 10 most dangerous diseases. According to statistical data, 6.3 out of 100,000 people die each year due to leukemia (CDC, 2016).

Leukemia is divided into several types based on cell maturity and hematopoiesis cell lineage. Based on cell maturity, leukemia is divided into acute and chronic. If the malignant cells are mostly immature (blasts), then the leukemia is classified as acute, whereas if the dominant cells are mature, it is classified as chronic leukemia. Based on cell lineage, leukemia is classified into myeloid leukemia and lymphoid leukemia (Lauder, et al., 2002). In acute leukemia, the abnormal blood cells fail to mature and are unable to carry out normal functions. Conversely, in chronic leukemia, the majority of cells retain their ability to function normally. The count of abnormal white blood cells increases more rapidly in acute leukemia compared to chronic leukemia, making acute leukemia more harmful.

Acute Myeloid Leukemia (AML) is the common type of leukemia in adults, with over 20,000 cases occurring annually in the United States. The disease is characterized by significant chromosomal translocations and mutations in genes that regulate hematopoietic proliferation and differentiation, resulting in the buildup of poorly differentiated myeloid cells. (Terwilliger and Abdul-Hay, 2017).

Red blood cells are important in transporting oxygen to body tissues. Abnormalities in red blood cells can provide important insights into the clinical conditions experienced by patients. Routine blood component examinations are commonly performed to determine whether erythrocyte, leukocyte, or platelet levels exceed normal limits. Various red blood cell parameters such as hematocrit, hemoglobin, and other erythrocyte indices can change due to hematopoietic disorders in AML patients. This systematic review study aims to collect and analyze various previous studies related to hemoglobin abnormalities in AML patients.

2. Materials And Methods

This study is a systematic review. The researchers reviewed several previous studies about abnormalities of hemoglobin levels in Acute Myeloid Leukemia patients.. The literature selection was using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, which aims to systematically explain the literature selection process. Previous studies obtained from online databases such as PubMed, ScienceDirect, and DOAJ.org using the keywords, individually or in combination with AND and OR: “Acute Leukemia,” “Acute Myeloid Leukemia,” “Hematological Profile,” “Hematological Parameters,” “Hemoglobin”.

Inclusion criteria were studies conducted on patients with AML and studies with observational design. AML patients with secondary disease or who have undergone a therapy were excluded. The quality assessment and risk of bias of the literature were evaluated using JBI critical appraisal tools for analytic cross-sectional studies. The data from the obtained literature were then extracted, including author names, the year of study, study setting, study design, and the number of study participants. Study outcome that extracted were median or mean and standard deviation (SD) of the hemoglobin levels.

The variables studied were hemoglobin levels, measured in g/L or g/dL, with the expected outcome being the mean or median value. The anemia classification criteria used the grading system from the US National Cancer Institute, as follows; Grade 0: Normal hemoglobin level (≥ 120 g/L for males, ≥ 110 g/L for females); grade 1 (Mild anemia): Hemoglobin level of 100-119 g/L; Grade 2 (Moderate anemia): Hemoglobin level of 80-99 g/L; Grade 3 (Severe anemia): Hemoglobin level of 65-79 g/L; Grade 4 (Life-threatening anemia): Hemoglobin level < 65 g/L

3. Results

3.1. Search Results

The literature was searched online using the databases PubMed, DOAJ, and ScienceDirect. The keyword search resulted in a total of 1,392 articles. After excluding duplicate articles, 1,347 articles remained. During the screening stage, 1,095 articles were excluded due to irrelevant titles and abstracts. Then, 189 full-text articles were reviewed based on the established exclusion criteria. The final result included 3 studies with observational research designs that met the inclusion and exclusion criteria.

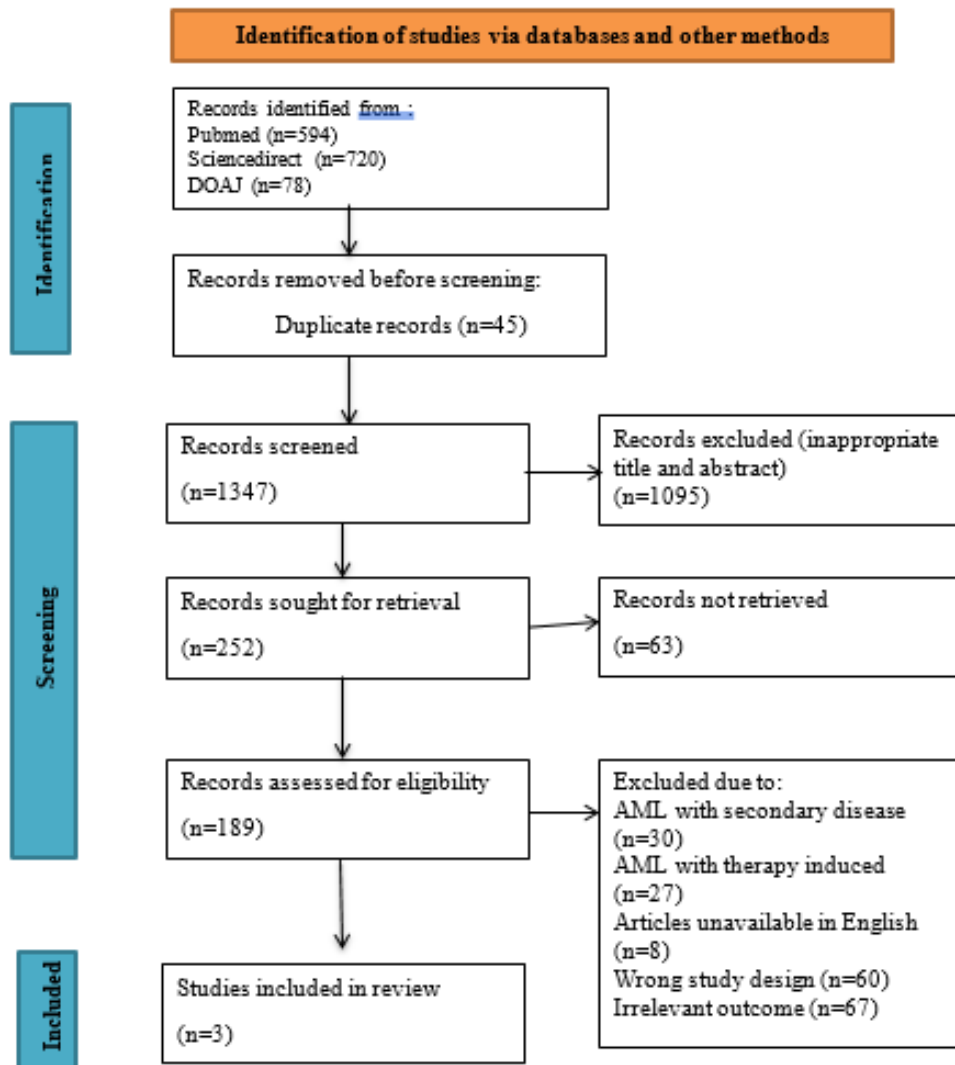


Figure 1. PRISMA Diagram

The three literature that we use in this review have a low risk of bias after being evaluated using the checklist provided by the Joanna Briggs Institute (JBI) critical appraisal tools for Analytic Cross-Sectional Studies.

3.2. Data Extraction

Data extraction was performed from the literature and subsequently entered into Excel. This review included three studies with a retrospective cross-sectional design conducted in three different countries. The total number of participants was 209, comprising 185 AML patients and 24 controls.

Table 1. Characteristics and Study Outcome

No	Authors	Demographic	Study Design	Participants	Outcome
					Hemoglobin
1	Suchismita et al., 2023	Bihar, India	Cross-Sectional	n=93	mean 7.2 ± 2.0 g/dL
2	Sanchez et al., 2015	Brazil	Cross-Sectional	AML (n=21)	median 7.7 (5.6-12.5) g/dL
				control (n=24)	median 13.55 (11.1-15.5) g/dL
3	Merdin et al., 2020	Ankara, Turki	Cross-Sectional	n=71	median 8.9 g/dL

In this review there are three studies included. The results of these three studies can be seen in table 1. A study conducted by Suchismita et al., 2023 in Bihar, India had 93 participants, with 37.6% of cases in women (n=35) and 62.4% in men (n=58). Participants' ages ranged from 11 to 80 years, with a mean age of 37.8 ± 13.3 years. The research results obtained on hemoglobin with a mean value of 7.2 ± 2.0 g/dL.

Research by Sanchez et al., 2015 was conducted at a center in Brazil on pediatric patients with confirmed AML, with a population aged 0 to 19 years. There were 21 AML patients evaluated, 11 women and 10 men with a median age of 6.83 (0.58-19.83) years. As controls, there were 24 healthy individuals with a median age of 9.67 (1.5-18.25) years. The research results showed that the mean hemoglobin value was 7.7 (5.6-12.5) g/dL in patients with AML, and 13.55 (11.1-15.5) g/dL in the control group. There was a significant difference between the hemoglobin levels of the control group and AML patients with $p < 0.0001$ as calculated by the Mann-Whitney Test.

Merdin et al., 2020 conducted research on AML patients with gene mutations before chemotherapy. Several parameters were analyzed, one of which was hemoglobin in 71 participants. The mean hemoglobin value was 8.9 g/dL.

4. Discussion

Acute Myeloid Leukemia (AML) is characterized by the proliferation of immature myeloid cells in the bone marrow. This infiltration can disrupt the normal production of other blood cells, including red blood cells which are responsible for transporting oxygen throughout the body. As a result, several clinical implications can occur, including anemia, which can cause symptoms such as fatigue, weakness and dyspnea (shortness of breath). This systematic review focuses on abnormalities in hemoglobin levels in patients with AML through several studies that have been conducted.

This systematic review determines the literature by searching online in databases using keywords that have been determined using the PRISMA flow diagram with inclusion and exclusion criteria that have been determined to reduce the risk of bias in the research. Three literature results were obtained after excluding other research that was not appropriate. Then an assessment of the quality of the literature was carried out using the JBI Critical Appraisal Tools for Cross-Sectional Studies to reduce the risk of bias. Then data extraction was carried out to retrieve data related to the characteristics of the study and the resulting outcomes, namely the median value or average value of hemoglobin levels in AML patients.

The three studies that included are research by Suchismita et al., 2023, Sanchez et al., 2015 and Merdin et al., 2020. There is one study with mean hemoglobin levels (Suchismita et al., 2023) and two studies with mean hemoglobin level (Sanchez et al., 2015 and Merdin et al., 2020). The studies that will be reviewed were carried out at centers in various countries, namely India (Suchismita et al., 2023), Turkey (Merdin et al., 2020) and Brazil (Sanchez et al., 2015).

The normal Hb level value in women is >11 g/dL and in men is >12 g/dL according to the US National Cancer Institute. These three studies showed low hemoglobin level measurement results. The results obtained by Suchismita et al., 2023 were a mean hemoglobin value of 7.2 ± 2.0 g/dL. Sanchez et al., 2015 reported a median value of hemoglobin of 7.7 (5.6-12.5) g/dL. Meanwhile, Merdin et al., 2020 reported a mean hemoglobin value of 8.9 g/dL.

Low hemoglobin levels in AML patients can be caused by many factors. In leukemia, bone marrow infiltration by abnormal leukemia cells can interfere with erythrocyte production. In addition, in AML myeloid progenitor cells fail to differentiate into mature cells, including erythrocytes. Several cases have been found where the body produces antibodies that attack red blood cells, causing hemolytic anemia. (Adimora et al., 2022)

Research conducted by Merdin et al., 2020 showed that the group of AML patients studied included moderate grade anemia (80-99g/L) whereas research conducted by Sanchez et al., 2015 and Suchismita et al., 2023 showed that AML patients are considered severe anemia (65-79g/L). Symptoms caused by anemia include weakness, fatigue, chest pain, headaches, difficulty breathing. The level of anemia in AML is important in determining the next therapy to be given.

This systematic review research is limited to the value of hemoglobin levels in AML patients obtained from the results of previous research. Further research is needed to determine the risk factors and causes related to low hemoglobin levels in AML patients.

5. Conclusion

Based on the problem formulation and objectives to be achieved and the results obtained, we concluded that AML patients have lower hemoglobin level than normal and included as a moderate to severe anemia. As a suggestion in future research, it is hoped that results can be grouped based on demographics, race, ethnicity and age to reduce bias. It is also need further prospective studies to confirm the prevalence and risk factors causing low hemoglobin levels in AML patients.

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References

- Adimora, I., & Rojas Hernandez, C. M., 2022, Thrombotic Thrombocytopenic Purpura Triggered by Acute Myeloid Leukemia: A Case Report. *The American journal of case reports*, 23, e935911. <https://doi.org/10.12659/AJCR.935911>
- CDC, 2016, Statistics of Cancers, Retrieved: April 25, 2018, from <https://gis.cdc.gov/Cancer/USCS/DataViz.html>
- Cossio, M. L. T. et al, 2016, Hoffbrands Essential Haematology, Wiley Blackwell doi: 10.1007/s13398-014-0173-7.2.
- Experts Committee on Cancer-Related Anemia, & Chinese Society of Clinical Oncology (CSCO), 2012, Clinical practice guidelines on cancer-related anemia (2012-2013 Edition), *Chinese clinical oncology*, 1(2), 18. <https://doi.org/10.3978/j.issn.2304-3865.2012.10.01>
- Faria, S. S. et al. 2016, 'The neutrophil-to-lymphocyte ratio: A narrative review', *PLoS ONE*, 9(6), doi: 10.1371/journal.pone.0101119.
- Jelkmann, W, 2011, Regulation of erythropoietin production. *Journal of Physiology*, 589(Pt 6), 1251-1258.
- Ketley, N, 2013, Wintrobe's Clinical Hematology, *Journal of clinical pathology*, doi: 10.1136/jcp.46.12.1142-c.
- Launder, T.M., Lawnicki, L.C., Perkins, M.L., 2002, 'Introduction to leukemia and the acute leukemias', In: Harmening DM, eds. *Clinical hematology and fundamental of hemostasis* edition 4, Philadelphia: FA, Davis Company, pp. 272-357.
- Lichtman, M.A and Liesveld, J.L, 2016, *Acute Myelogenous Leukemia, USA : Williams Hematology Ninth Edition*, pp. 1373-1436.
- Longo, D. L. et al., 2013, *Harrison's Hematology and Oncology 2 Edition*, McGraw- Hill Education.
- Mayo Clinic, 2018, Complete blood count (CBC), Retrieved: April 25, 2018, from <https://www.mayoclinic.org/tests-procedures/complete-blood-count/about/pac-20384919> (Diakses: 25 April 2018).
- Medline Plus, 2017, Complete Blood Count: MedlinePlus Lab Test Information, Retrieved: April 26, 2018, from <https://medlineplus.gov/labtests/completebloodcount.html>
- Mehta, A. B. and Hoffbrand, A. V. 2014, *Haematology at a Glance*, doi: 10.1046/j.1365-2257.2000.00136.x.
- Merdin, A., Dal, M. S., Çakar, M. K., Yildiz, J., Ulu, B. U., Batgi, H., Tetik, A., Seçilmiş, S., Darçin, T., Şahin, D., Bakirtaş, M., Başçi, S., Yiğenoğlu, T. N., Baysal, N. A., İskender, D., & Altuntaş, F. (2020). Analysis of pre-chemotherapy WBC, PLT, monocyte, hemoglobin, and MPV levels in acute myeloid leukemia patients with WT1, FLT3, or NPM gene mutations. *Medicine*, 99(14), e19627. <https://doi.org/10.1097/MD.00000000000019627>
- Naeim F, Rao P.N, Grody, W.W, 2008, *Acute Myeloid Leukemia*, Hematopathology ed. 1. Amsterdam, The Netherlands : Academic Press Elsevier pp. 1-26 & pp. 207-255.
- National Institute of Health, 2015, 'Understanding Your Complete Blood Count', National Institute of Health Clinical Center, 000, pp. 1–5. Retrieved: April 26, 2018, from https://www.cc.nih.gov/ccc/patient_education/pepubs/cbc.pdf.
- Purnomo BH, Sutaryo, Ugrasena I, 2005, *Buku Ajar Hematologi-Onkologi Anak*, Jakarta: Ikatan Dokter Anak Indonesia.
- Sanchez, F.L.F.Z., Nitsch, T.M., Vilela, M.M.S., Sgarbieri, V.C., Comparison of biochemical and immunological profile of pediatric patients with acute myeloid leukemia in relation to healthy individuals, *Jornal de Pediatria*, Volume 91, Issue 5, 2015, Pages 478-484, ISSN 0021-7557, <https://doi.org/10.1016/j.jped.2014.12.004>.
- Shuchismita, S., Jamal, I., Raman, R. B., & Choudhary, V. (2022). Clinico-Hematological Profile of Acute Leukemia Cases in Bihar: A Multiparameter Study in a Tertiary-Care Hospital. *Journal of laboratory physicians*, 15(1), 84–89. <https://doi.org/10.1055/s-0042-1757233>
- Terwilliger, T. and Abdul-Hay, M, 2017, 'Acute Lymphoblastic Leukemia A Comprehensive Review and 2017 Update', *Blood Cancer Journal*, 7, e577.
- World Health Organization, *The Global Prevalence of Anemia in 2011*, Geneva : World Health Organization.
- Zhou, X. et al, 2014, 'Prognostic value of PLR in various cancers: A meta-analysis', *PLoS ONE*, 9(6). doi: 10.1371/journal.pone.0101119.