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Etiology of Pancytopenia in Tabriz Shahid Ghazi Hospital: A Cross-sectional Study in Iran

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Abstract: *Objective:* Pancytopenia is characterized by a reduction in all three types of blood cells: erythrocytes, leukocytes, and platelets. Pancytopenia is caused by a wide range of diseases, leading to diagnostic conundrums. These causes can range from drug reactions to life-threatening diseases such as aplastic anemia and leukemia. This study aims to investigate the causes of pancytopenia, specifically focusing on age and gender differences among patients. *Methods:* This cross-sectional study includes patients of all ages diagnosed with pancytopenia, as indicated by a CBC/H1 showing a WBC count less than 4,000/μL, platelet count less than 150,000/μL, and hemoglobin levels below 12 g/dL in women and less than 13 g/dL in men. The study only included patients with pancytopenia who underwent bone marrow examination and were not subjected to chemotherapy or radiation therapy. *Results:* A total of 133 patients with pancytopenia were included in the study. The average age was 47.35 ± 17.62 years old, with 66% of the participants being male and 34% being female. Acute leukemia, specifically acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL), was identified as the primary cause of pancytopenia, accounting for 31.5% of cases. Megaloblastic anemia was the second most common cause, accounting for 30% of cases, followed by aplastic anemia at 7.5%. *Conclusion:* Pancytopenia, a condition marked by the decrease in both erythrocytes and leukocytes as well as thrombocytes, can arise from a myriad of causes. The main findings of this study revealed that megaloblastic anemia, acute myeloid leukemia (AML), and acute lymphoid leukemia (ALL) were the most common causes. Significantly, a considerable proportion of cases of pancytopenia can be attributed to acute leukemia. Hence, expeditious and accurate diagnosis is imperative and has the potential to save lives in such cases.

Keywords: Pancytopenia; Leukemia; Anemia; Bone marrow; Blood cells

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1. Introduction

Pancytopenia poses a diagnostic challenge in the field of clinical hematology. Pancytopenia refers to a decline in the number of all three types of blood cells, namely erythrocytes, leukocytes, and platelets. This condition

can have life-threatening consequences due to the development of anemia, increased susceptibility to infections, and a tendency to bleed excessively.

Pancytopenia can result from one or more of the following mechanisms [1]:

(1) Bone marrow infiltration or replacement: This can occur in various disorders such as hematologic malignancies (such as leukemia, lymphoma, multiple myeloma, and myelodysplastic syndrome), metastatic cancer, myelofibrosis, and infectious diseases (such as miliary tuberculosis and fungal infections).

(2) Bone marrow aplasia: The causes of marrow aplasia include nutritional disorders such as deficiencies of vitamin B12 or folate, aplastic anemia, infectious diseases like HIV, viral hepatitis, parvovirus B19, immune destruction, and medication.

(3) Excessive destruction of blood cells can occur in conditions such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and ineffective hematopoiesis, which includes myelodysplastic syndrome and megaloblastic disorders.

(4) Excessive sequestration of blood cells may be caused by hypersplenism, which can result from liver cirrhosis, storage diseases, lymphoma, or autoimmune disorders.

The level of circulating blood cells is determined by a delicate equilibrium between blood cell production, distribution in other organs, and continuous cell destruction, such as white blood cells fighting infections, platelets used in blood clots, and cellular senescence [2–5].

The frequency of various disorders leading to pancytopenia is influenced by several factors, including geographical distribution, which impacts factors such as nutritional status, climate, and the prevalence of infections, as well as demographic factors such as age patterns and genetic variation. Pancytopenia can vary from a benign drug reaction to a severe medical condition, such as aplastic anemia and acute leukemia.

Despite extensive research on the causes of pancytopenia, there are still limitations in fully comprehending its range of causes. Different methods are used to diagnose the cause of pancytopenia in patients. Neumann and Bizzozero's research established the correlation between blood and bone marrow [6,7]. Neumann observed in 1868 that bone marrow played a crucial role in the production of red blood cells [6]. The cause of pancytopenia can often be determined from the examination of a peripheral blood smear (PBS) [8-10]. Key findings in this test include:

(1) Alterations in the morphology and size of red blood cells;

(2) The presence of immature and atypical leukocytes;

(3) Platelet size variations, as evidenced by megaloblastic changes and blast cells.

Following this, bone marrow biopsy becomes crucial in further understanding the etiology of pancytopenia. While some experts consider marrow examination important for accurate diagnosis, there is ongoing debate about its necessity in all cases of pancytopenia [11,12]. Finally, based on bone marrow aspiration results, the causes of pancytopenia are generally categorized into two groups, namely hypocellular and cellular [13–16].

Given these factors and the paucity of research on pancytopenia in the area, the study has chosen to investigate the etiology of the condition at Tabriz Shaheed Ghazi Hospital, a referral center for hematology and oncology in northwest Iran.

2. Materials and methods

This cross-sectional study was conducted at Tabriz Shahid Ghazi Hospital, a referral center for patients from Iran's northwest area. The study aimed to discover the causes of pancytopenia and was carried out from December 2015 to December 2016, spanning a one-year period. All these patients suffering from pancytopenia were referred to Tabriz Shahid Ghazi Hospital for the intent of hospitalization and took part in the study. A comprehensive history, which included information about drug consumption, was recorded for all cases,

regardless of age and gender. All patients with pancytopenia underwent a physical examination, peripheral blood smear (PBS), and complete blood count (CBC/H1). Additional inquiries were undertaken to assess the underlying reason for pancytopenia. The study included patients who met specific criteria, which consisted of having a white blood cell count below 4,000/µL, a platelet count below 150,000/µL and hemoglobin levels below 12 g/dL in women and below 13 g/dL in men [1,17,18]. All these patients underwent bone marrow aspiration. Each patient was provided with a detailed explanation of the procedure in their own language. Before conducting bone marrow aspiration, a peripheral blood smear was prepared. The study excluded patients with pancytopenia caused by prior chemotherapy or radiotherapy and those who did not undergo bone marrow examination. The identification of these patients occurred during routine visits to Shahid Ghazi Hospital. The team analyzed the patients' information and final diagnosis after filling out a data-collecting form.

The data were examined using descriptive statistics (mean, standard deviation, and variance analysis) in SPSS version 16. Afterward, frequency and diagnostic-related traits were analyzed. In addition, descriptive statistics, such as percentages, frequencies, and mean ± standard deviation (SD) were used to display the data.

3. Results

The study included 133 individuals, 87 (66%) males and 46 (34%) females (**Figure 1**). The mean age of the patients was 47.35 ± 17.62 years old, ranging from 16 to 80 years old (**Figure 2**).

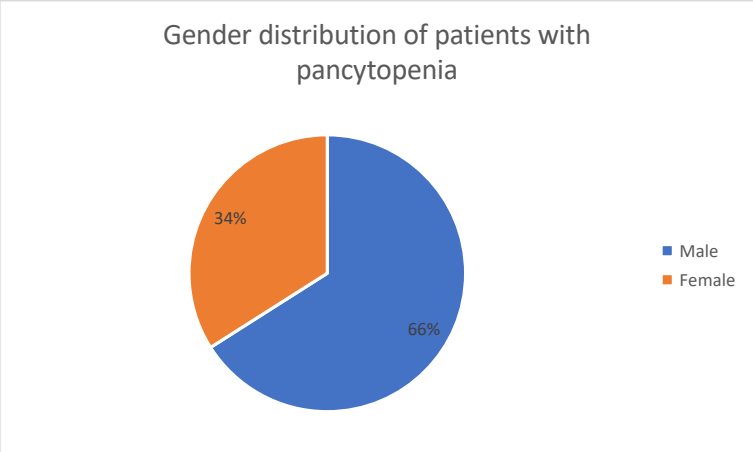

Figure 1. Gender distribution of cases of pancytopenia in the present study.

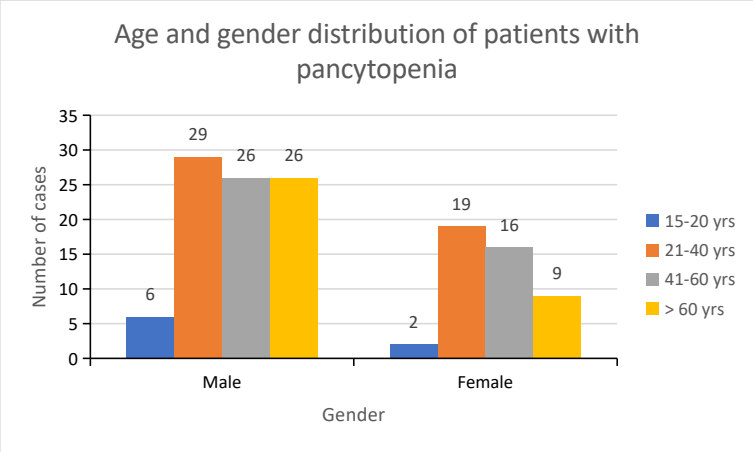

Figure 2. Age and gender distribution of patients with pancytopenia in the present study.

Table 1 demonstrates that in this study, the three most common factors contributing to pancytopenia were megaloblastic anemia, which accounted for 30% of cases, acute myelogenous leukemia (AML) at 21%, and acute lymphocytic leukemia (ALL) at 10.5%. The study indicates that the primary cause of pancytopenia was acute leukemia (AML and ALL), which affected a total of 42 patients, consisting of 26 males and 16 females. In addition, hairy cell leukemia (HCL) was diagnosed in two patients. In total, 44 individuals were diagnosed with leukemia, accounting for 33% of the cases of pancytopenia in this study. Among these cases, there were 28 males and 16 females.

Table 1. Etiologies of pancytopenia in the present study

Etiology	Number of cases	Percent (%)
Megaloblastic anemia (MA)	40	30
Acute myelogenous leukemia (AML)	28	21
Acute lymphocytic leukemia (ALL)	14	10.5
Aplastic anemia (AA)	10	7.5
Myelodysplastic syndrome (MDS)	8	6.1
Cirrhosis	6	4.5
Peripheral pancytopenia with normal bone marrow (non-cirrhosis)	10	7.5
Multiple myeloma (MM)	4	3
Sepsis	3	2.3
Viral infectious	3	2.3
Hairy cell leukemia (HCL)	2	1.5
Pharmaceutical causes (non-chemotherapy)	2	1.5
Myelofibrosis	1	0.75
Systemic lupus erythematosus (SLE)	1	0.75
Histiocytosis	1	0.75

Figures 3–**6** demonstrate that the predominant cause of pancytopenia varied across different age cohorts in this study. ALL was the primary cause in the age group 15–20 years old. MA was found to be the predominant cause of anemia in the age groups of 21–40, 41–60, and over 60 years old.

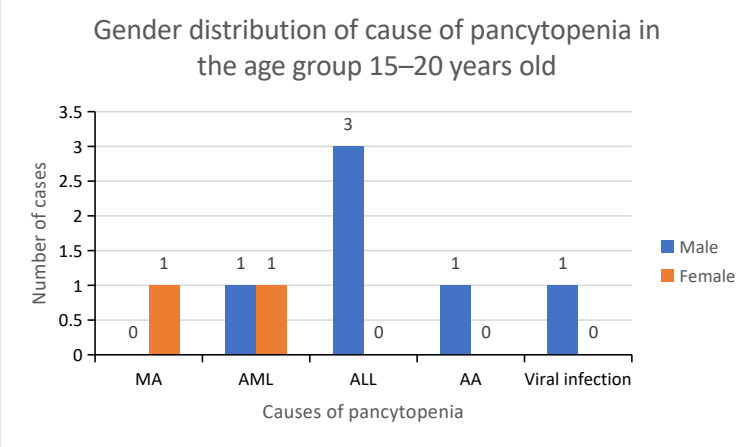

Figure 3. Gender distribution of cause of pancytopenia in the age group 15–20 years old. Abbreviation: MA, megaloblastic anemia; AML, acute myelogenous leukemia; ALL, acute lymphoid leukemia; AA, aplastic anemia

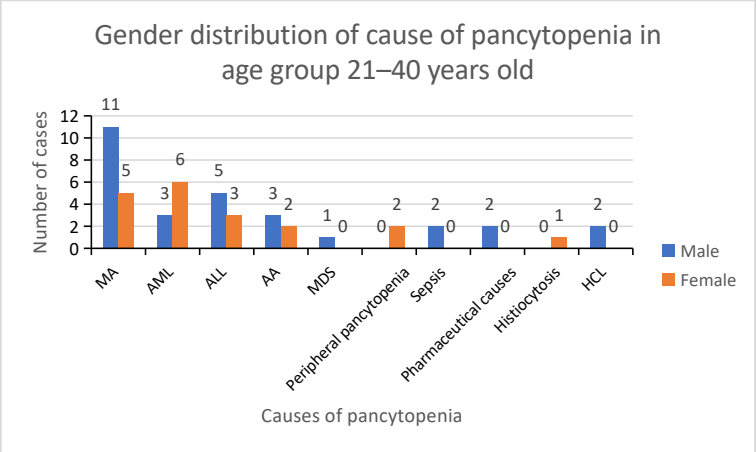

Figure 4. Gender distribution of cause of pancytopenia in the age group 21–40 years old. Abbreviation: MA, megaloblastic anemia; AML, acute myelogenous leukemia; ALL, acute lymphoid leukemia; AA, aplastic anemia; MDS, myelodysplastic syndrome; HCL, hairy cell leukemia

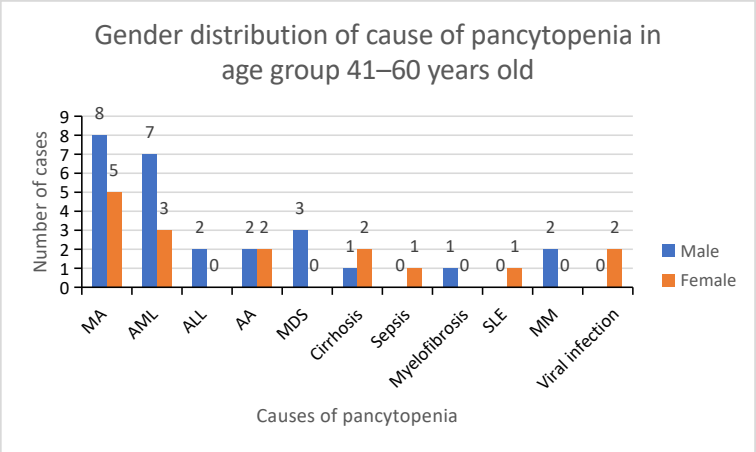

Figure 5. Distribution of causes of pancytopenia by gender in the age range of 41 to 60. Abbreviation: MA, megaloblastic anemia; AML, acute myelogenous leukemia; ALL, acute lymphoid leukemia; AA, aplastic anemia; MDS, myelodysplastic syndrome; SLE, systemic lupus erythematosus; MM, multiple myeloma

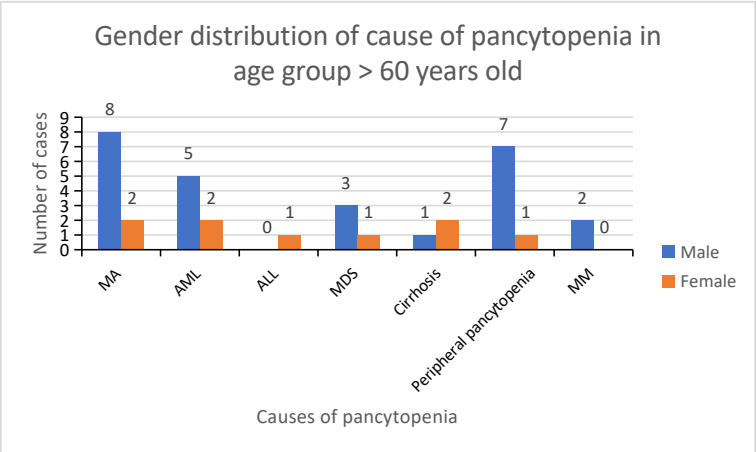

Figure 6. Distribution of causes of pancytopenia by gender in the age range of over 60. Abbreviation: MA, megaloblastic anemia; AML, acute myelogenous leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma

There were 56 cases of hematopoietic neoplasms, which made up 42% of all occurrences of pancytopenia. The distribution of these cases is as follows:

(1) Acute leukemia (AML and ALL) accounted for 31.5% of cases.

(2) Myelodysplastic syndrome (MDS) accounted for 6% of cases.

(3) Multiple myeloma (MM) accounted for 3% of cases.

(4) Hairy cell leukemia (HCL) accounted for 1.5% of cases.

Below is a list of the important hematological parameters that were examined in this study.

(1) Hemoglobin: The majority of patients showed hemoglobin levels ranging from 6 to 9 grams per deciliter (g/dL). Two cases revealed the lowest hemoglobin level of 3.5 g/dL. One of these instances was observed in a patient diagnosed with megaloblastic anemia, and the other was observed in a patient diagnosed with acute myeloid leukemia (AML), as described in **Table 2** and depicted in **Figure 7**.

Table 2. Values of hemoglobin in cases of pancytopenia in the present study

Hemoglobin (g/dL)	Number of cases	Percentage (%)
0–3	0	0
3–6	18	13.6
6–9	82	61.6
9–12	33	24.8

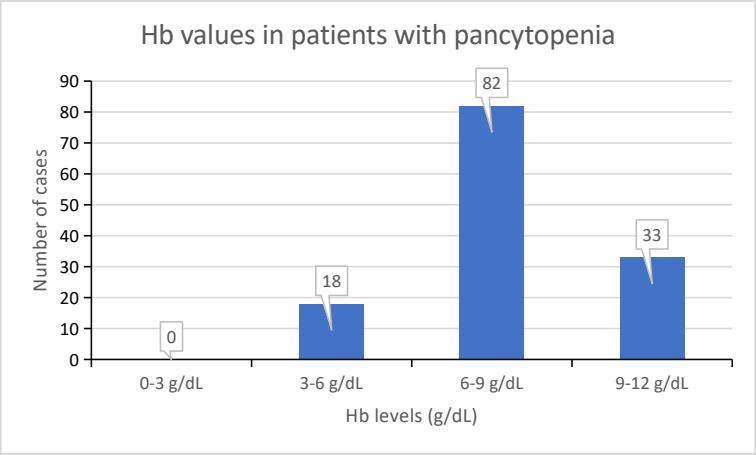

Figure 7. Values of hemoglobin in cases of pancytopenia in the present study

(2) White blood cells (WBC): The majority of patients showed a white blood cell count within the range of 1,000–2,000 cells/µL. The case of drug-induced pancytopenia (non-chemotherapy) displayed the lowest count of 370 cells/µL, as shown in **Table 3** and **Figure 8**.

Table 3. Values of WBC count in cases of pancytopenia in the present study

WBC (cells/µL)	Number of cases	Percentage (%)
0–1,000	4	3
1,000–2,000	55	41.5
2,000–3,000	46	34.5
3,000–4,000	28	21

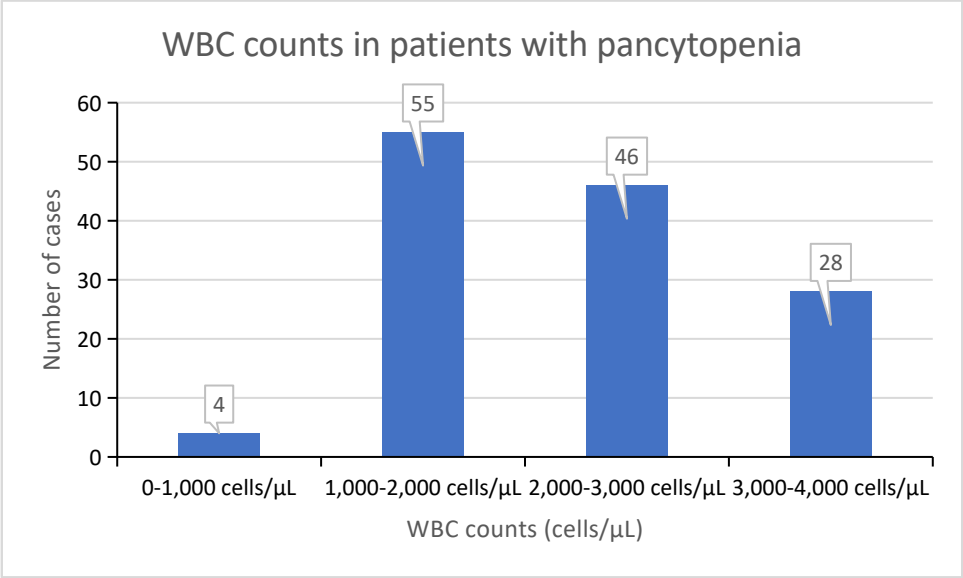

Figure 8. Values of WBC count in cases of pancytopenia in the present study

(3) Platelet: The majority of patients had a platelet count ranging from 50,000 to 100,000 per microliter. Two instances were seen where the platelet count reached a minimum of 6,000/µL. One case was associated with acute lymphoblastic leukemia (ALL), whereas the other case had peripheral pancytopenia with normal bone marrow, as shown in **Table 4** and **Figure 9**.

Table 4. Values of platelet count in cases of pancytopenia in the present study

Platelet count (/µL)	Number of cases	Percentage (%)
0–50,000	43	32.3
50,000–100,000	73	54.9
100,000–150,000	17	12.8

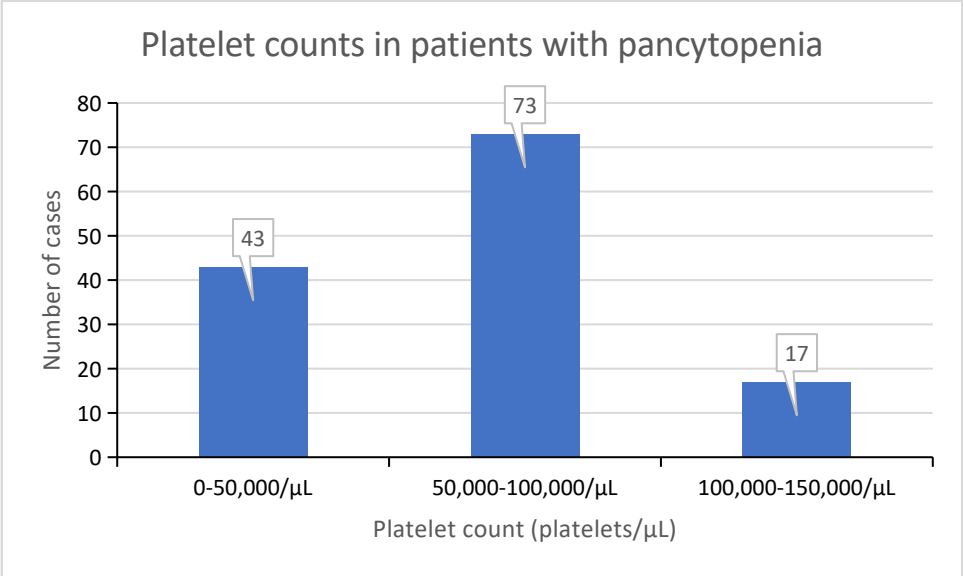

Figure 9. Values of platelet count in cases of pancytopenia in the present study

The hematological parameters in the most frequent causes of pancytopenia showed that the lowest hemoglobin value (3.5 g/dL) was observed in two cases: MA and AML. The lowest average white blood cell (WBC) count of 1,834/μL was seen in patients with AA, while the lowest average platelet count of 8,000/μL was found in patients with ALL (**Table 5**).

Table 5. Hematological parameters in more common causes of pancytopenia

Etiology	Hemoglobin (g/dL)			White blood cells (/μL)			Platelet (/μL)		
	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean
MA	3.5	11.6	7.5	15,000	149,000	83,108	870	3,890	2,303
AA	7	10.9	8.4	8,000	110,000	44,800	970	3,000	1,834
Acute leukemia	3.5	11.4	7.83	10,000	149,000	55,021	970	3,920	2,020
AML	3.5	11.4	7.85	10,000	140,000	61,509	970	3,920	1,969
ALL	5.5	10.8	7.8	10,000	149,000	43,667	1,000	3,100	2,108

4. Discussion

Pancytopenia is a common hematological occurrence in our clinical practice and should be addressed when a patient presents with unexplained anemia, fever, and bleeding tendencies. There is a lack of research on the prevalence of the causes of pancytopenia in Iran. This study aimed to examine the etiology of pancytopenia in patients referred to Shaheed Ghazi Hospital, a specialized facility for Hematology and Oncology located in Tabriz City. An analysis was conducted to determine the causes of pancytopenia in these patients, taking into account their age and gender. A total of 133 patients with pancytopenia were included in the study conducted at Shaheed Ghazi Hospital. These patients were diagnosed with 15 distinct causes of pancytopenia.

The predominant etiologies of pancytopenia in the study were identified as follows: megaloblastic anemia (30%), acute myeloid leukemia (21%), acute lymphoid leukemia (10.5%), and aplastic anemia (7.5%). Furthermore, the mean age of the patients was 47.35 ± 17.62 years old. Of the patients, 66% were male and 34% were female, resulting in a male-to-female ratio of 1.94:1. Among the 133 patients, 8 were younger than 20 years old, accounting for just 6% of the cases. Patients aged 21 to 40 years old comprised 36% of the total, while those between 41 and 60 years old totaled 32%. The remaining 26% of patients were above 61 years old. Additionally, the current study found that hematological neoplasms (AML, ALL, MDS, and HCL) were the cause of pancytopenia in 56 instances, which constitutes 42% of the total. Leukemia was the cause of pancytopenia in 33% of the cases. The most common cause of pancytopenia in patients who were brought to the hospital was acute leukemia, comprising 31.5% of all cases.

There was an overlap between the main causes of cytopenia, and the routine hematological tests that were conducted lacked specificity. The peripheral blood smear was found to be effective in identifying the cause of the condition in patients with megaloblastic anemia and leukemia [19]. Prior studies have emphasized the importance of conducting a bone marrow examination on patients diagnosed with pancytopenia syndrome [20–22]. Within the realm of hematology, bone marrow aspiration is an essential diagnostic procedure used to assess various cases of cytopenia. Bone marrow aspiration is a crucial diagnostic technique in the field of hematology that aids in the evaluation of different instances of cytopenia. The advantages of bone marrow examination include its non-invasive nature, cost-effectiveness, and ability to yield prompt and dependable outcomes. Conducting a bone marrow aspiration is adequate for the diagnosis of nutritional anemia and for the initial identification of leukemia [6]. Although bone marrow aspiration study is not frequently conducted for suspected

cases of megaloblastic anemia, it is recommended in situations where the diagnosis is uncertain or when immediate treatment is necessary, and hematological procedures are unavailable [6].

Table 6. Comparison with different studies

No.	Authors	Place	Age (years)	Cases no.	First common cause	Second common cause	Third common cause	Mean age or most commonly affected age group (years)	M:F
1	Present study	Iran	All ages	133	Acute leukemia (31.5%)	MA (30%)	AA (7.5%)	47.35 ± 17.62	1.99:1
2	Karsing *et al.* [23]	India	All ages	60	MA (66%)	AA (18.3%)	Malaria (5%)	41	1.3:1
3	Khunger *et al.* [24]	India	2–70	200	MA (72%)	AA (14%)	Acute leukemia (5%)	3th decade	1.2:1
4	Khodke *et al.* [25]	India	3–69	50	MA (62%)	AA (20%)	MM (5.7%)	12–30	1.3:1
5	Kumar *et al.* [26]	India	All ages	166	AA (29.51%)	MA (22.28%)	Sub leukemic leukemia (12.04%)	-	-
6	Gayathri and Rao [27]	India	All ages	104	MA (74.04%)	AA (18.36%)	Sub leukemic leukemia (3.85%)	42	1.2:1
7	Varma and Dash [28]	India	Adults	202	AA (40.6%)	MA (23.26%)	AML (12.8%)	-	-
8	Khan *et al.* [11]	Pakistan	All ages	160	AA (37.5%)	MA (13.75%)	Acute leukemia (13.75%)	35	1.5:1
9	Kumar *et al.* [29]	Pakistan	All ages	62	MA (41.9%)	AML (27.4%)	AA (19.4%)	37.76 ± 16.38	1.38:1
10	Agarwal *et al.* [30]	India	All ages	70	Malaria (30%)	AA (14.28%)	Tuberculosis (12.86%)	1–30	1:1.2
11	Santra and Das [31]	India	13–65	111	AA (20.72%)	Cirrhosis (11.71%)	Kala-azar (9%)	36.9	1.47:1
12	Gupta *et al.* [19]	India	All ages	169	MA (37.78%)	Mixed nutritional deficiency anemia (15.98%)	AA (11.24%)	11–20	1.2:1
13	Jella *et al.* [10]	India	< 18	56	MA (42.9%)	AA (23.2%)	Malaria (7.1%)	34.9 ± 4.3	1.43:1
14	Patel *et al.* [8]	India	< 12	50	MA (58%)	AA (12%)	Cirrhosis (4%)	21–30	1.7:1
15	Tilak *et al.* [17]	India	5–70	77	MA (68%)	AA (7.7%)	Malaria	-	-
16	Jalaei-Khuu and Keihani [32]	Iran	All ages	188	Acute leukemia (35.6%)	AA (22.3%)	MA (14.9%)	2th decade	1.38:1

Studies conducted in Pakistan and India have consistently shown that megaloblastic anemia is the primary underlying cause of pancytopenia, as indicated in **Table 6**. Acute leukemia was the predominant etiology of pancytopenia in the study, with megaloblastic anemia being the subsequent cause. Gayathri BN *et al.* (2015) documented a significantly elevated prevalence rate of 74.04% for megaloblastic anemia [25]. The variability in the occurrence of different diagnostic entities causing pancytopenia can be attributed to differences in methodology and strictness of diagnostic criteria, geographical location, duration of observation, genetic variations, and varying exposure to toxic substances in the bone marrow [27]. This study highlights the importance of pancytopenia in different hospital environments, with a particular emphasis on comprehending

the distinct causes associated with each type of hospital.

It is essential to acknowledge the study's limitations. While the sample size is small, the data collected are specific to the only oncology referral center in northwest Iran. To obtain more conclusive findings, it is advisable to undertake additional studies with a larger sample size and also to conduct systematic reviews in this field. Considering the therapeutic significance of the subject, it is vital to perform further studies in this sector to enhance early diagnosis.

5. Conclusion

Pancytopenia, a condition marked by the decrease in all types of blood cells, is a medical condition that often requires hospitalization. The etiology of this condition is multifactorial, and the reported cause is usually dependent on the specific healthcare center. The most common cause of pancytopenia in general hospitals is frequently claimed to be infections. Nevertheless, at the Tabriz Shaheed Ghazi Hospital, the most frequently seen causes of pancytopenia are acute leukemia and megaloblastic anemia. Significantly, acute myeloid leukemia (AML) is the dominant form of acute leukemia at this center, representing 21% of cases, which is approximately twice the rate of acute lymphoid leukemia (ALL), which stands at around 10.5%. This discrepancy underscores the diversity in the etiology of pancytopenia among various healthcare institutions. It is important to rapidly detect and diagnose pancytopenia, focusing on identifying its specific cause. Early intervention can result in early treatment of treatable conditions, which can significantly improve patient outcomes.

Ethics approval

The study received approval from the Medical Ethics Committee of Tabriz University of Medical Sciences and Health Services (IR.TBZMED.REC.94/3-7/23, 1394/08/30). Furthermore, all procedures were carried out in strict adherence to all relevant regulations and protocols.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Conceptualization and design: Hossein Azari Bostanabad, Babak Nejati, Ali Esfahani
Analysis and interpretation of data: Hossein Azari Bostanabad
Data collection: Hossein Azari Bostanabad, Mohammad Hossein Hosseini
Participation in drafting or revising the article: Safa Mousavi, Sadra Sarandili

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