

## The Relation of Baseline Serum Albumin with the Duration of Neutropenia after Induction Chemotherapy in Adult Acute Leukaemia

Muhammad Nadeem, Nayab Khan, Muhammad Khalid Piracha\*, Farhan Ahmed Majeed\*\*, Ayesha Halim\*\*\*

Department of Medical Oncology, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, \*Department of Medical Admin, Combined Military Hospital, Gilgit/National University of Medical Sciences (NUMS) Pakistan, \*\*Department of Surgery, Combined Military Hospital, Multan/National University of Medical Sciences (NUMS) Pakistan, \*\*\*Department of Nutrition, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

### ABSTRACT

**Objective:** To determine the relation of baseline serum albumin levels with the duration of neutropenia after induction chemotherapy in acute leukaemia.

**Study design:** Prospective longitudinal study.

**Place and Duration of Study:** Department of Medical Oncology, Combined Military Hospital, Rawalpindi Pakistan, Dec 2018 and Dec 2020.

**Methodology:** Ninety-one patients with newly diagnosed acute leukaemia who were planned to receive induction chemotherapy were included. Before starting chemotherapy, blood counts and serum albumin levels were determined in each patient. The tests were monitored during treatment, and the duration of days when the patient experienced neutropenia was noted.

**Results:** The mean age of participants was 29.70±9.50 years. 64(70.3%) were males and 27(29.7 %) were female. At presentation, the mean white blood cell (WBC) count in peripheral blood was 16.70±39.60 x10<sup>9</sup>/L. 29 (31.9%) patients had hypoalbuminemia with serum albumin <3.5g/dL, while 62 (68.1%) patients had normal serum albumin ≥3.5g/dL. The mean duration of neutropenia in the Low Albumin Group was 8.20±5.30 days. The mean duration of neutropenia in Normal Albumin (≥3.5g/dL) Group was 7.50±6.30 days. There was no Statistical difference between low serum albumin and the duration of neutropenia (*p-value* 0.605).

**Conclusion:** This study shows that the pre-chemotherapy serum albumin level has no significant relation with the duration of neutropenia experienced by the patient after induction chemotherapy of acute leukaemia.

**Keywords:** Albumin, Induction chemotherapy leukaemia, Neutropenia, Nutritional status.

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### INTRODUCTION

Leukaemia is a heterogeneous group of disorders originating from bone marrow stem cells. Acute leukaemia results from immature hematopoietic stem cells due to their malignant transformation followed by clonal proliferation.<sup>1</sup> Though it needs to be clearly understood, the pathogenesis of this transformation is thought to be a multistep process.<sup>2</sup> According to the US SEER database, in 2021, leukaemia-related estimated deaths were 3.9% of all cancer deaths.<sup>2,3</sup> Acute leukaemia is classified according to its differentiation along the myeloid or lymphoid lineage in the bone marrow (BM). The historical WHO classification system revised in 2008 defines the criterion for diagnosis of AML as more than 20% blasts in marrow or blood.<sup>4</sup> It requires that ALL diagnoses be deferred if there are fewer than 20% blasts in the bone marrow.

Immunophenotyping, molecular markers and cytogenetics now play a vital role in diagnosing and characterising acute leukaemia.<sup>5</sup> The management of acute leukaemia requires intensive chemotherapy intended to kill all the leukemic clones. This is achieved in phases, and the first phase is called induction chemotherapy. This is the most delicate part of the treatment as the patient is exposed to fatal infectious complications till the stem cell recovers.<sup>6</sup> Stem cell and cellular differentiation recovery depends on nutritional factors and the patient's baseline health status. Empirical broad-spectrum antimicrobials and antifungals are used to bridge the interval of recovery of stem cells.<sup>7</sup>

This study aimed to determine if pre-treatment serum albumin levels could be used to predict the occurrence and duration of neutropenia in a patient with acute leukaemia. The importance of determining this is that if found true, it could serve as a simple guiding tool for patients at a higher risk of developing

**Correspondence:** Dr Muhammad Nadeem, Department of Medical Oncology, Combined Military Hospital, Rawalpindi Pakistan  
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neutropenic complications. This would allow for better and judicious allocation of resources towards infection prophylaxis and treatment.

**METHODOLOGY**

The prospective longitudinal study was conducted at the Department of Medical Oncology, Combined Military Hospital, Rawalpindi Pakistan, from December 2018 and December 2020 after approval from the Ethical Review Board was sought (IRB CMH Rawalpindi number 02/37/20/54 dated 24-7-2020). The sample size was calculated using the WHO sample size calculator by using proportion of hypoalbuminemia in patients with acute leukaemia undergoing induction chemotherapy as 30% and precision required as 10 %.<sup>8</sup> The sample was gathered by using the non-probability consecutive sampling method.

**Inclusion Criteria:** Patients of either gender aged 15-45 years, presenting at the Outpatient Department with newly diagnosed acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) and planned for standard induction therapy were included.

**Exclusion Criteria:** Patients with a history of antecedent myelodysplastic syndrome, previously treated, relapsed or refractory leukaemia and patients with significant co-morbidities affecting treatment outcomes like pre-existing diabetes mellitus, hepatic, renal or cardiac dysfunction and patients treated with palliative rather than curative intent were excluded.

All the patients were briefed about the study, and informed verbal and written consent was obtained. All patients were admitted to the ward, and treatment and evaluation were conducted indoors. The diagnosis and type of Acute Leukaemia was based on bone marrow biopsy, including immunophenotyping and genetic studies according to the WHO classification.<sup>3</sup> Haemoglobin level (Hb) and White Blood Cell (WBC) count were obtained from Complete Blood Counts. Serum Albumin levels were also recorded before the initiation of chemotherapy. The serum albumin levels were defined as low <3.5g/dL and normal >3.5g/dL.<sup>9</sup>

The patients received standard induction chemotherapy as per the type of leukaemia. Standard D3A7 was used for all acute myeloid leukaemia except AML-M3, where standard AIDA protocol was given. In ALL, patients received standard BFM protocol phase 1 regimen B. After chemotherapy, the days of neutropenia were defined as per IDSA guidelines as the number of days when the patient had an absolute neutrophil count (ANC) of 500 cells/mm<sup>3</sup> or less than

1,000 cells/mm<sup>3</sup> with an anticipated decline to less than 500 cells/mm<sup>3</sup> within 48 hours.<sup>10</sup> All the data was recorded on formatted data sheets.

The data was analysed using the computer software Statistical Package for Social Sciences (SPSS) version 24. Continuous variables were expressed as Mean±Standard deviation (SD), while frequency and percentage were calculated for categorical variables. Independent samples t-test was applied to assess the mean difference of serum albumin with duration of myelosuppression. The *p*-value of ≤0.05 was considered statistically significant.

**RESULTS**

Ninety-one patients receiving chemotherapy for newly diagnosed acute leukaemia were included in this analysis. Among them, 64 (70.3%) were males, and 27(29.7 %) were female patients. The mean age was 29.7±9.5 years. 43(47.3%) patients had various subtypes of Acute Myeloid Leukaemia (AML, except AML-M3), 17(18.7%) patients had Acute Promyelocytic Leukaemia (APL or AML-M3), and 31(34%) were diagnosed with Acute Lymphoblastic Leukaemia (ALL). The patient characteristics are shown in Table-I.

**Table-I: Characteristics of study patients (n=91)**

Characteristics	Values
Age (years)	29.70±9.50 years
<b>Gender</b>	
Male	64(70.3%)
Female	27(29.7 %)
<b>Disease</b>	
Acute Myeloid Leukaemia	43(47.3%)
Acute Promyelocytic Leukaemia	17(18.7%)
Acute Lymphocytic Leukaemia	31(34%)

The mean patient BSA was 1.31±0.199. At presentation, the mean haemoglobin (Hb) level was 8.90±1.70g/dL (min=4, max=12.6), mean white blood cell (WBC) count in peripheral blood was 16.7±39.6 x10<sup>9</sup>/L (min=0.2, max=200), mean serum albumin levels were 36.8±5.9g/dL. At the beginning of treatment, 29(31.9%) patients had serum albumin <3.5g/dL, while 62(68.1%) patients had serum albumin ≥3.5g/dL. After chemotherapy was initiated, the mean duration of neutropenia in the Low Albumin (<3.5g/dL) Group was 8.21±5.36 days (min1, max21). The mean duration of neutropenia in Normal Albumin (≥3.5g/dL) Group was 7.50±6.34 days (min0, max30). On comparison of the baseline serum albumin value with the duration of neutropenic days, it was found not to be significantly related to the *p*-value of 0.605 shown in Table-II.

**Table-II: Comparison of Baseline Serum Albumin Levels with duration of Neutropenia (n=91)**

Duration of Neutropenia	Baseline Serum Albumin Levels		p-value
	Low (<3.5 g/dL) (n=29)	Normal (≥3.5g/dL) (n=62)	
	8.21±5.36 days	7.50±6.34 days	0.605

## DISCUSSION

Acute leukaemia in adults is not associated with promising outcomes. The anti-leukemic therapy is very toxic and exhausting. The most intense phase is the induction phase of treatment. Here, the goal is to clear the bone marrow of the leukemic clone and achieve remission. However, this goal is achieved at the cost of severe myelosuppression lasting for one to three weeks, often requiring multiple blood product transfusions and antimicrobial support.<sup>10</sup> This study aimed to determine whether the baseline value of serum albumin taken as an index of nutritional status relates to the duration of myelosuppression after induction chemotherapy in adult acute leukaemia.

In this study, a total of 91 newly diagnosed patients with acute leukaemia were admitted to receive induction chemotherapy, the protocols being the standard for the type of leukaemia diagnosed. Pre-treatment investigations revealed that most patients were anaemic at presentations with a mean haemoglobin (Hb) level of 8.9±1.7g/dl (min=4, max=12.6). Anaemia is a common finding in acute leukaemia attributable to multiple mechanisms ranging from nutritional to metabolic and leukaemia-related causes. A study by Pattnik et al. in India 2019 reported an overall proportion of anaemia to be 80% in ALL.<sup>11</sup> In our study, the mean WBC count in peripheral blood before the beginning of treatment was 16.7±39.6 x10<sup>9</sup>/L but ranged from a minimum of 0.2 x10<sup>9</sup>/L to a maximum value of 200 x10<sup>9</sup>/L. Such clinical observations have been reported in literature where there is a huge variability in initial cell counts of patients at presentation. Jaime-Perez and colleagues in Mexico in 2019 reported that leucocytosis and leukopenia were present in 36.6% and 36.1% of cases of acute leukaemia, respectively.<sup>12</sup> In a review article by Keller in Switzerland in 2019, it was found that serum albumin values are good predictors of surgical outcomes, prognosis and mortality in various clinical scenarios.<sup>13</sup> In our study, 29(31.9%) patients were found to have hypoalbuminemia (serum albumin level less than 3.5g/dL) at presentation. The blood counts were checked daily once the patients were started on

induction chemotherapy. The duration of neutropenia was recorded for each patient and subsequently analysed. In the patient group with low serum albumin <3.5g/dL, the mean duration of neutropenia was 8.2±5.3 days. On the other hand, in the patient group with normal serum albumin ≥3.5g/dL, the mean duration of neutropenia was 7.5±6.3 days. Comparative analysis of both groups using independent samples t-test revealed that the effect of serum albumin on the duration of neutropenia was not statistically significant ( $p$ -value>0.05). Morison at Minneapolis in 2014 also showed that while low serum albumin had a positive relation with the duration of fever in neutropenic patients, it did not affect the duration of neutropenia itself.<sup>14</sup> By contrast, Komrokji *et al.* at Tampa in 2009 studied the prognostic value of serum albumin in relapsed AML and concluded that it has a prognostic role, which should be validated in newly diagnosed cases.<sup>15</sup> Then, Khan and colleagues at Alabama in 2011 reported that serum albumin is an independent prognostic factor for overall survival in patients with acute myeloid leukaemia at diagnosis.<sup>16</sup> However, neither of them studied the effect of serum albumin on neutropenia, which we have studied in our study. Another interesting study was conducted by Esfahani and colleagues in 2014, which showed that serum albumin, along with other markers, was predictive of the duration of neutropenic fever in patients with acute leukaemia during induction chemotherapy.<sup>17</sup> Although the design of this study was similar to our study, however, they had different results. Another study by Ghafoor and colleagues at Rawalpindi in 2020 showed that the nutritional status of paediatric acute myeloid leukaemia patients significantly impacted treatment-related mortality.<sup>18</sup> However, they assessed the nutritional status according to Z-score calculations & serum albumin was not studied.

Thus, it is clear that the baseline health and nutritional status of a patient at the time of diagnosis of acute leukaemia can greatly determine their ability to tolerate and respond to chemotherapy. It has also been shown to contribute to their overall survival. However, the measurement of baseline health can be done on different parameters. This study aimed to determine whether a patient's serum albumin level can be used as a predictor of the duration of neutropenia and neutropenic fever. However, it was not found to be significantly correlated. There is conflicting data in this regard, with most work leaning towards it being able to determine overall survival rather than neutropenia duration. More research on a larger scale

can be conducted in future to determine if, indeed, there is any connection between the duration of neutropenia and the degree of hypoalbuminemia in a patient with acute leukaemia.

### CONCLUSION

Neutropenia and myelosuppression are the most common complications affecting patients receiving treatment for acute leukaemia. It can have far-reaching and often devastating effects on the patient's prognosis, especially in the scenario of neutropenic sepsis. Various efforts have been made to devise simple yet effective methods of predicting which patients are more prone to prolonged neutropenia and, hence, more susceptible to infections. In this research, serum albumin level was found not significantly related to the duration of neutropenia; hence, it cannot be used as a reliable predicting tool in clinical practice.

**Conflict of Interest:** None.

### Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MN & NK: Conception, study design, drafting the manuscript, approval of the final version to be published.

MKP & FAM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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