Assessment of Baseline Nutritional Status, Vitamin B12, and Folate Levels in Patients with Acute Leukemia and Their Effect on Initial Treatment Outcome: A Prospective Observational Study

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Abstract

Introduction Poor nutrition is a common finding in patients with acute leukemia, affecting disease progression, treatment outcome, and survival. Overall nutritional status and micronutrients status evaluation may be an important step in management of acute leukemia.

Objective The objective of this study was to investigate baseline nutritional status, vitamin B12, and folate levels in patients with acute leukemia at the time of admission before starting chemotherapy and their initial treatment outcome.

Materials and Methods This was a prospective observational study. We assessed the pretreatment nutritional status of 73 patients by body mass index (BMI), serum vitamin B12 using a two-step chemiluminescent microparticle immunoassay, and serum folate using electrochemiluminescence by Cobas e411 analyzer before initiation of induction chemotherapy and evaluated for treatment response at the end of induction chemotherapy.

Results Out of a total of 73 patients, 51 (69.8%) completed induction chemotherapy, 36 (49.3%) showed complete remission, and 15 (20.5%) were in incomplete remission. Of the remaining 22 (30.1%) patients, 11 (15.1%) died due to toxicity during therapy. The mean values of baseline BMI, serum vitamin B12, and folate was 20.46 kg/m^2, 956.04, and 13.52 ng/mL, respectively. There was no significant association between vitamin B12 (p-value = 0.609) and folate (p-value = 0.404) deficiency and the response to treatment.

Conclusion Baseline nutritional status, serum vitamin B12, and folate levels have no significant role in induction outcome in response to treatment, including mortality in patients with acute leukemia.

Keywords

- acute leukemia
- folate
- induction chemotherapy
- micronutrient status
- vitamin B12

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Introduction

Poor nutrition is a common finding in patients with hematological malignancy, affecting disease progression and survival.[1] Human beings require macronutrients (carbohydrates, fats, and proteins) and micronutrients (vitamins, minerals, and other biochemicals) for nearly all metabolic and developmental processes. Micronutrients are critical for several vital functions in our body. Their deficiency is a significant health problem in India.[2] Data on micronutrient status in people are not available; however, recent studies from India have highlighted that people suffer from micronutrient deficiency.[3] Earlier reported data indicate that 47% of the north Indian population had a deficit of vitamin B12.[4] This may be due to multiple reasons: a significant proportion of the Indian population, 29% is vegetarian,[5] and other factors such as poor nutrition, malabsorption, and other gastrointestinal causes may also be responsible.[6,7] The elderly and alcoholics are prone to vitamin B12 due to poor oral intake.[8,9] Various studies suggest that vitamin B12 deficiency is more common in hematological malignancies than nonhematological diseases.[10,11] Earlier studies indicate that folate deficiency exists in 40% of the Indian population.[12–14] Inadequate serum folate levels may increase cancer risk, including hematological malignancies.[15–17]

Vitamin B12 and folate act as coenzymes that participate in one-carbon metabolism involved in DNA methylation and DNA synthesis.[18,19] Inadequate intake of these micronutrients may disrupt one-carbon metabolism resulting in the risk of developing hematological malignancies.[16] Hence, the need of the hour is to evaluate the baseline status of vitamin B12 and folate in patients with hematological malignancies.

Very few studies have been performed for determining the micronutrient status (vitamin B12 and folate) in acute leukemia, and mostly, these have been done in the pediatric population.[20–22] It is essential to know the levels of nutritional status and their impact on the treatment and quality of life. Therefore, in this study, we aimed to investigate baseline nutritional status, serum vitamin B12 levels, and folate levels in patients with acute leukemia and evaluate their effect on response to therapy.

Materials and Methods

Study Participants

This study included patients with newly diagnosed acute leukemia presenting to the clinical haematology department of a tertiary care teaching and referral institute in northern India, from September 2018 to September 2019.

Inclusion and Exclusion Criteria

Patients suffering from acute leukemia and age older than 13 years, attending the department of clinical hematology OPD were consecutively included in this study. Prior to enrollment of the patient, written informed consent was obtained from him/her or legally authorized relative.

Patients who were unwilling to give written informed consent, those who were already on chemotherapy and using drugs containing vitamin B12 and folate, and those who had undergone gastric or ileocecal resection (which could potentially interfere with the absorption of vitamin B12) were excluded from the study.

Outcome Measures

Primary outcome measure was to study the association of nutritional status, vitamin B12, and folate levels with induction remission status of acute leukemia patients. Secondary outcome measure was to study the association of nutritional status, vitamin B12, and folate levels with induction-related death.

Data Collection

We collected baseline nutritional data of patients at the time of their admission in the ward before starting chemotherapy. Measurement of height (in cm), weight (in kg), body mass index (BMI), socioeconomic condition,[23] physical activity level,[24] food habits, serum protein, and serum albumin were recorded. Calculation of calorie and protein intake was done. Weight was measured in kilogram using a weighing scale, and height was measured in centimeter by using a stadiometer. Data on weight and height were collected to the nearest 0.1 kg and 1 cm, respectively. BMI was calculated using the formula: person's weight in kilogram divided by his/her height in meter squared. BMI is a calculated number that represents a person's level of fat or obesity level. BMI level was classified as: underweight (BMI $<$18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI $>$30).[25]

To calculate calorie and protein, dietary guidelines of National Institute of Nutrition (NIN) Hyderabad, India was followed. Patients' 24-hour dietary recall was maintained according to feedback given by their attendant. The food exchange method (NIN) was used for the calculation of nutrients. The food frequency table was also recorded at the time of admission to get detailed information about patients' food habits, likes, and dislikes.

Complete hemogram (hemoglobin, total leukocyte count, differential leukocyte count, platelets, total red blood cells), liver function test (serum bilirubin, SGOT, SGPT, serum alkaline phosphatase), kidney function test (serum urea, serum creatinine, uric acid), serum electrolyte, serum calcium, serum magnesium, and serum phosphorus were done; enzyme-linked immunosorbent assay was used to test viral markers including hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus.

Criteria for a complete remission of acute leukemia was bone marrow aspiration and biopsy $<$5% blasts at the end of induction chemotherapy. Death due to toxicity during induction chemotherapy was defined as death associated with neutropenia (absolute neutrophil count $<$1,000) and fever or other features of sepsis after initiation of induction chemotherapy until postinduction recovery of peripheral blood counts.

Sample Collection for Micronutrients

For estimation of micronutrients, a 2-mL blood sample was collected in plain vials from individuals. Serum levels of vitamin B12 were determined by using a two-step chemiluminescent microparticle immunoassay, and levels were expressed in picogram/milliliter (pg/mL). The serum level of folate was measured by using Cobas e411 analyzer, and levels were expressed in nanogram/milliliter (ng/mL). The cutoff value for serum vitamin B12 was <203 pg/mL, while it was <4 ng/mL for folate to determine the deficiency levels.[26]

Statistical Analysis

The data were entered in MS Excel spreadsheet, and analysis was done using Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, Illinois, United States). Categorical variables were presented in numbers, and percentages (%) and continuous variables were presented as mean ± standard deviation (SD). Qualitative variables were compared using the chi-square test. A p-value of <0.05 was considered statistically significant.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki 1964, as revised in 2013. Ethics committee approval was obtained from the King George's Medical University institutional ethics committee dated August 28, 2018, number 91st ECM II A/P5 prior to enrollment of the patient, and written informed consent was obtained from him/her or legally authorized relative.

Results

Patient Characteristics

Seventy-three newly diagnosed patients enrolled between September 2018 and September 2019 were included in the study. There were 44 (60.3%) males and 29 (39.7%) females with an M:F ratio of 1.5:1. All the patients belonged to either lower, 47 (64.4%), or middle socioeconomic strata, 26 (35.6%). The mean (SD) age of patients was 30.32 (14.95) years (►**Table 1**). The average mean (SD) of anthropometric variables such as weight, height, and BMI of these patients was 52.29 (11.07) kg, 180.12 (166.30) cm, and 20.46 (3.96)kg/m^2, respectively. ►**Table 1** depicts the general baseline characteristics of the patients.

Baseline Nutritional Status

The mean values of serum vitamin B12 and folate levels were 956.04 pg/mL and 13.52 ng/mL, respectively. The majority of patients had good nutritional status 43 (58.9%), and 22 (30%) were underweight. Fifty-three (72%) patients had normal levels (>203) of vitamin B12, whereas 20 (27%) were deficient (≤203). Sixty-five (92%) patients had normal levels (>4) of folate, and only 6 (8%) were deficient (≤4). Normal levels of serum protein (≥6) and serum albumin (>3.5) were seen in 53 (72%) and 46 (63%) patients, respectively. Deficient serum protein (<6) and serum albumin (≤3.5) was seen in 20 (27.3%) and 27 (36%) patients, respectively.

Remission Status and Mortality

Of 73 patients, 44 (60.3%) were having acute lymphoblastic leukemia and 29 (39.7%) acute myeloid leukemia (AML). Fifty-one (69.8%) patients completed induction chemotherapy, 49.3% (36) showed complete remission, and 20.5% (15) incomplete remission. Of the remaining 30.1% (22) patients, 15.1% (11) died due to toxicity during therapy, 8.2% (6) deaths were due to other reasons, and 5 (6.8%) patients left against medical advice.

Effect of Pretreatment Nutritional Status, Vitamin B12, and Folate on Response to Treatment

We analyzed nutritional status and their response to induction treatment. Undernutrition had no significant association (p-value = 0.104) with the response of the treatment (►**Table 2**). The pretreatment nutritional value of vitamin B12 (p-value = 0.609), folate (p-value = 0.404), serum total protein (p-value = 0.736), and serum albumin (p-value = 0.312) had no significant association with response to induction chemotherapy.

We also analyzed the effect of age, sex, dietary habit, segment, disease, serum vitamin B12, and serum folate levels on the response in terms of remission status. In univariate analysis of different parameters with response to treatment, we found no significant difference (►**Table 3**).

Discussion

We investigated nutritional status, vitamin B12, and folate levels in patients with acute leukemia before induction chemotherapy. We found that baseline prenutrition status had no significant association with the response to induction chemotherapy or induction-related mortality.

Normal levels of vitamin B12 were found in 72% of patients with acute leukemia, while 91.5% had normal folate levels. Horie et al had shown that serum vitamin B12 levels were normal in 80% of the patient, similar to our study. However, only 50% of the patients had normal values of folate level, which is contradictory to our study.[27] This may be due to multiple reasons. One is that 82% of the patients in our study were of younger age group (mean age 30.3 years), whereas in the earlier study, the patients were older individuals (mean age 62.5 years). In older individuals, folate concentration in serum and cerebrospinal fluid falls and plasma homocysteine rises with age, contributing to the aging process. Other reasons such as low dietary intake, malabsorption, drugs, and increased demand in the older individual may result in folate deficiency.[28,29]

Most of the patients who had complete or incomplete remission had normal serum vitamin B12 and folate values. In our study, deficiency of vitamin B12 (p-value = 0.609) and folate (p-value = 0.404) was not associated with treatment response in the patients (►**Table 2**). In a study by Hoogstraten et al, most of the complete remission cases had normal vitamin B12 and folate values. Similar to our study, no such correlation between the status of disease and serum vitamin B12 levels was found, while low levels of folate were observed in those with incomplete remission.[16]

The association between vitamin B12 and folate deficiency with leukemia treatment outcome was not found in our study. On the other hand, a study done in the pediatric population investigating the effect of vitamin B12 and folate deficiency on

Table 1 Baseline characteristics of the enrolled patients

Characteristic	Categories	Number (73)	Percentage
Age (y)	Mean ± SD	30.32 (14.95)	
	Range	13–70	
Sex	Male	44	60.3
	Female	29	39.7
Socioeconomic condition	Low	47	64.4
	Middle	26	35.6
Physical activity level	Active	11	15.1
	Low	28	38.4
	Moderate	34	46.6
Dietary habit	Nonvegetarian	44	60.3
	Vegetarian	29	39.7
Addiction	No addiction	49	67.1
	Smoking	5	6.8
	Alcohol	2	2.7
	Tobacco	17	23.3
Nutritional status			
BMI	Normal	43	58.9
	Obese	2	2.7
	Overweight	6	8.2
	Underweight	22	30.1
Calorie (kcal)	Mean ± SD	1127.49 (414.50)	
Protein (g)	Mean ± SD	24.82 (10.02)	
Serum protein (g/dL)	Mean ± SD	6.53 (1.12)	
	Range	3.83–8.62	
Serum albumin (g/dL)	Mean ± SD	3.65 (0.63)	
	Range	1.80–4.80	
Vitamin B12 (pg/mL)	Mean ± SD	956.04 (1,178.41)	
	Range	83–5,960	
Folate (ng/mL)	Mean ± SD	13.52 (9.63)	
	Range	2.2–41.2	

Abbreviations: BMI, body mass index; SD, standard deviation.

induction chemotherapy showed that it was positively correlated with the outcome of the disease. Children deficient in folate and vitamin B12 showed incomplete bone marrow remission and death due to induction chemotherapy compared with those with normal levels.[21]

BMI, serum protein, serum albumin, and hemoglobin indicate the nutritional status of a person. In the present study, the average BMI of patients before chemotherapy was 20.4, which indicates normal weight status. This study indicates that there was no association between nutritional status, BMI (p-value = 0.493), serum protein (p-value = 0.806), serum albumin (p-value = 0.523), and hemoglobin (p-value = 0.281) with the response of the diseases. This agrees with a study by Medeiros et al, which reported no association between the impact of BMI on the rates of complete remission, induction death, resistant disease, and overall survival in AML patients.[30] On the other hand, studies investigating nutritional status in children and hematological malignancies showed mixed results. Tandon et al showed that 66% of children were undernourished, and baseline nutritional deficiencies do not affect the outcome of disease during induction chemotherapy.[21] A study by Shane stated that the prevalence of malnutrition in children is very high and has a significant role in the outcome of life-threatening complications during their treatment.[19] Malnutrition is also a significant factor influencing treatment planning and therapeutic decisions.[31]

For proper management of any malignancy, adequate nutrition is crucial, as it may affect the prognosis of the disease. In our study, the patients were not taking proper

Table 2 Effect of pretreatment nutritional status on response after induction chemotherapy

		Response						*p*-Value
		Complete remission		Incomplete remission		Death due to toxicity		
		N	%	*N*	%	*N*	%	
Vitamin B12	≤203	12	33.3%	4	26.7%	2	18.2%	0.609
	>203	24	66.7%	11	73.3%	9	81.8%	
Folate	≤4	2	5.6%	1	7.1%	2	18.2%	0.404
	>4	34	94.4%	13	92.9%	9	81.8%	
Total protein	<6	10	27.8%	3	20.0%	2	18.2%	0.736
	≥6	26	72.2%	12	80.0%	9	81.8%	
Albumin	<3.5	12	33.3%	4	26.7%	6	54.5%	0.312
	≥3.5	24	66.7%	11	73.3%	5	45.5%	
BMI	<18.5	7	19.4%	5	33.3%	0	0%	0.104
	≥18.5	29	80.6%	10	66.7%	11	100.0%	

Abbreviation: BMI, body mass index.

Table 3 Effect of other parameters on remission status

Parameters	Unadjusted (univariate)	
	OR (95% CI)	*p*-Value
Age (≤50)	0.954 (0.164–5.561)	0.958
Sex (male)	1.179 (0.342–4.063)	0.794
Dietary habit (NV)	1.750 (0.512–5.978)	0.372
Socioeconomic condition (low)	0.250 (0.062–1.038)	0.056
Disease (ALL vs. AML)	3.429 (0.969–12.137)	0.056

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; NV, nonvegetarian; OR, odds ratio.

diet; hence, their nutritional status was not good, and however, we found that their average BMI was normal. According to the European Society for Clinical Nutrition and Metabolism guidelines on nutrition in cancer, the nutritional requirement of cancer patients and those not suffering from the disease is the same (around 25–30 kcal/kg/d).[32] The protein requirement is estimated to be 1.5 g/kg/d. In our patients, the average calorie and protein intake per day was 1,127 kcal and 24.82 g, respectively, which is very low compared with the above guidelines. In our study, 60.3% of patients were nonvegetarian, which may be the reason for a normal or elevated level of vitamin B12 (72%) and folate (91.5%).

Vitamin B12 and folate are involved in red blood cell maturation; hence, it becomes vital to analyze the levels of these micronutrients in acute leukemia. Other micronutrients such as selenium, zinc, and copper are responsible in protection against oxidative stress in leukemia patients. A study by Zuo et al demonstrated that there are low selenium, zinc, and high copper status in leukemia patients. The low levels of zinc and high level of copper ratio showed an unfavorable prognosis of acute leukemia.[33] Similar to this, a study by Valadbeigi et al also estimated serum selenium, zinc, and copper levels in acute leukemia patients and showed similar results.[34] In contrast, a study by Akhgarjand et al analyzed levels of serum zinc and copper in patients with acute leukemia and observed a significant increase in serum zinc and a significant decrease in serum copper.[35]

The present study reveals that baseline nutritional status and micronutrient status do not impact short-term outcomes in patients with acute leukemia. The current study's limitations were that the sample size was small, and the long-term outcome was not analyzed. Further studies are needed with a long-term follow-up and larger sample size, comprising people from across the globe, especially from those regions where the incidences of vitamin B12 and folate deficiencies are reported to be higher.

Conclusion

This study results show that nutrition does not impact treatment outcomes of patients with acute leukemia in the short term, including remission status and mortality during induction therapy. However, long-term studies are required to study this association of nutritional status with the survival rate and overall outcome in the long term.

Note
The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

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Conflict of Interest
None declared.

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