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# Differences in Parathyroid Hormone-Related Peptide and Serum Electrolytes in Acute Leukemia Patients

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## ABSTRACT

Acute leukemia is a clonal malignancy of myeloid or lymphoid precursor cells. Parathyroid hormone-related protein (PTHrp) is an 84 amino acid protein released by the parathyroid glands. Serum electrolyte disturbances are common in acute leukemia patients. This study aimed to determine the difference in the levels of PTHrp and serum electrolytes (sodium, potassium, calcium ion) in acute leukemia patients. An observational analytic research, cross-sectional approach was performed at the Dr. Moewardi Hospital in Surakarta between June and August 2019 with 43 subjects. Acute leukemia, based on the FAB classification, is divided into two groups (myeloid and lymphoid lineage). The serum was used for measurement of PTHrp levels with enzyme immunoassay (ELISA) principle (the Rayto RT-2100C) and serum electrolyte with the Ion Selective Electrode (ISE) method (AVL analyzer). The data were tested by comparison test and ROC curve, p was significant if <0.05, and the confidence interval was 95%. Acute leukemia subjects comprised 24 lymphoid lineages (55.8%) and 19 (44.2%) myeloid lineages subjects. The mean age was 25 (7-47) years, with 18 (41.9%) male subjects and 25 (58.1%) female subjects. The mean sodium level was 136 (132-140) mmol/L, with a mean level of 134.38±4.75 mmol/L and 137.00 (121-143) mmol/L in the lymphoid and myeloid lineage groups, respectively. The cut-off point for serum sodium levels was 135.5 mmol/L, with an AUC of 0.679, a sensitivity of 73.7%, and a specificity of 67.7%. There was a significant difference in serum sodium electrolyte levels in acute leukemia patients (p=0.046) but not in acute leukemia patients' serum potassium, calcium ion, and PTHrp levels (p=0.415; p=0.912 and p=0.293, respectively). Further research was needed in the chronic leukemia population and other research variables related to electrolyte balance.

**Keywords:** Acute leukemia, lymphoid lineage, myeloid lineage, PTHrp, serum electrolytes

## INTRODUCTION

Laboratory evaluation of patients with suspected acute leukemia malignancy is complex and has evolved rapidly with the involvement of more advanced laboratory techniques.[1] The World Health Organization (WHO) in 2014 in the World Cancer Report reported the incidence of leukemia per 100,000 patients was 3.9 in females and 5.6 in males, with a leukemia mortality rate of 2.8 in females and 4.1 in males. Acute leukemia can be classified according to French-American-British (FAB) or WHO. In general, acute leukemia is divided into Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), and acute leukemia of ambiguous lineage or Mixed-Phenotype Acute Leukemia (MPAL).[1]

Serum electrolytes are minerals that carry an electric charge in the body, consisting of potassium (K), sodium (Na), phosphate (Ph), calcium ion (Ca), magnesium (Mg), and others. Electrolyte disturbances can occur in patients with cancer or malignancy. This disorder is a complication in patients with malignancy, which needs further attention. Several things, such as the underlying malignancy, effects of therapeutic agents, or disease response, can cause electrolyte abnormalities in malignancy. Common electrolyte disorders include hypokalemia, hypercalcemia, hyponatremia, hypomagnesemia, and phosphorus disorders.[2]

The prevalence of hypokalemia in one study was 12%, whereas hypomagnesemia was approximately 61%. The causes of hypokalemia in cancer patients are multifactorial, including malnutrition due to poor food intake, transcellular potassium shift, and loss of gastrointestinal and renal fluid. Among the types of hematological malignancies, AML is frequently associated with hypokalemia. In addition, previous studies found heme malignancy to be the third cause of potassium incidence, or low potassium.[2] Hypercalcemia rarely occurs in pediatric patients with ALL. The mechanism of osteolytic lesions and hypercalcemia induced by ALL is unclear. Still, it is most likely related to the production of a factor by

tumor cells that activate osteoclasts known as parathyroid hormone-related peptides (PTHrP). Hypercalcemia is commonly seen in some cases of adult hematologic malignancies such as adult T-cell lymphoma and multiple myeloma; however, hypercalcemia is not usually associated with childhood cancer.[3]

Parathyroid hormone (PTH) is synthesized and secreted by the primary cells of the parathyroid glands. Intact PTH is a single-chain polypeptide with a molecular weight of 9500Da and consists of 84 amino acids. This parathyroid hormone comes from a more significant precursor, pre-pro-PTH, with 115 amino acids, which undergo two consecutive cleavages on the terminal amino sequence, the first to produce an intermediate precursor (pro-PTH) and the second to the hormone itself. Pro-PTH that reaches circulation is immediately converted to PTH and other products.[4]

A large retrospective study with over 6,000 pediatric cancer patients reported electrolyte disturbances in 2,816 patients with acute leukemia or lymphoma. In contrast, a < 0.3% incidence of hypercalcemia at diagnosis was reported in the acute leukemia or lymphoma group.[5] A retrospective study of baseline pre-B ALL cells with 83 patients reported a higher incidence of hypercalcemia of 4.8%.[6] Electrolyte abnormalities are common and can present complications in malignant patients. These abnormalities are often known for their etiology and can be anticipated and appropriately treated if the diagnosis is made early and accurately.[2]

It is well known that expensive, irregular, and invasive tests such as peripheral blood smear, bone marrow puncture, or flow cytometry are needed to differentiate lymphoid and myeloid leukemias. However, clinical pathologists should have expertise in these tests; therefore, a simple, inexpensive, regular marker is required. Based on the background above, the authors wanted to examine the differences in PTHrp and serum electrolytes (sodium, potassium, and calcium ions) levels between lymphoid and myeloid lineage acute leukemia patients.

## METHODS

This research was an observational analytic study with a cross-sectional approach. The population of this study was all acute leukemia subjects who underwent laboratory tests at the Clinical Pathology Installation of Dr. Moewardi General Hospital in Surakarta. The inclusion criteria of this study were patients with acute leukemia diagnosed by clinicians based on the results of routine blood tests, peripheral blood microscopy, bone marrow morphology, and immunophenotyping using the EuroFlow antibody panels criteria and already signed the informed consent. The exclusion criteria of this study were hemolyzed, lipemic, and icteric samples. Research subjects were selected by a total sampling of 43 people from June to August 2019. The research form, anamnesis, physical examination, and vital signs recorded data of subject identity. A total of 8 mL of venous blood was used, including 3 mL of ethylenediaminetetraacetic acid (EDTA) blood for routine blood tests, peripheral blood imaging, and immunophenotyping, while 5 mL of blood without anti-coagulant for measurement of electrolyte and serum PTHrp levels. A blood draw of 2 mL of bone marrow aspiration was used for bone marrow morphology examination. No fasting was required, including subjects with new undiagnosed patients. Blood was collected before patients got any treatments for leukemia. The variables of this study were PTHrp and serum electrolyte (sodium, potassium, and calcium ion) levels. PTHrp levels were measured using the enzyme immunoassay (ELISA) method with the Rayto RT-2100C (China). Electrolyte levels were measured with the ion selective electrode method with AVL 9180 electrolyte analyzer (US).

Data on the characteristics of the research subjects were presented in mean and standard deviation. Data normality was analyzed using Shapiro Wilk ($p>0.05$). Independent sample T-test was used to analyze the difference between the two variables in the ratio on data with normal distribution, and the Mann-Whitney test was used on data with abnormal distribution. In addition, nominal data were analyzed with the Chi-Square test. Statistical analysis was processed using a computer program; a 95% confidence interval was used and significant if $p<0.05$. Dr. Moewardi General Hospital Ethical Committee approved this study with number 795/VI/HREC/2019. Informed consent was obtained from all research subjects. The patient's identity was kept confidential, and all costs related to the research were the authors' responsibility.

## RESULTS AND DISCUSSIONS

This study involved 43 subjects with acute leukemia. Acute leukemia has a rapid clinical course and is known to have high mortality and morbidity. Acute leukemia is classified based on its lineage into lymphoid lineage, myeloid lineage, and MPAL.[1,7-9] A total of 43 acute leukemia subjects in this study were divided into the lymphoid lineage group of 24

(55.8%) subjects and the myeloid lineage group of 19 (44.2%) subjects. Lymphoid lineage in this study involved 7 (16.3%) subjects with ALL L1, and 17 (39.5%) subjects with L2, while myeloid lineage with M0, M1, M2, M3, M4, M5, M6, and M7 was 2 (4.7%), 1 (2.3%), 4 (9.3%), 2 (4.7%), 9 (21%), 0 (0%), 1 (2.3%), and 0 (0%) subjects, respectively (Table 1).

**Table 1.** Lineage classification of acute leukemia

| Types of Acute Leukemia | Total (n) | Percentage (%) |
|---|---|---|
| **Lymphoid lineage** | | |
| L1 | 7 | 16.3 |
| L2 | 17 | 39.5 |
| L3 | 0 | 0 |
| **Myeloid lineage** | | |
| M0 | 2 | 4.7 |
| M1 | 1 | 2.3 |
| M2 | 4 | 9.3 |
| M3 | 2 | 4.7 |
| M4 | 9 | 21.0 |
| M5 | 0 | 0 |
| M6 | 1 | 2.3 |
| M7 | 0 | 0 |

The Shapiro-Wilk normality test was used because the number of subjects was less than 50. The normality test results showed that data of Hb and potassium levels had normal distribution, while age, leukocyte count, platelet count, sodium, calcium ion, and PTHrp had abnormal distribution.

The results of this study showed that the number of acute leukemia subjects with an average age (25th-75th percentile) was 25 (7-47) years. The average age of the lymphoid lineage and myeloid lineage groups was 8 (2-43) years and 40.9±18.6 years, respectively, with a significant difference (p=0.0001) (see Table 2 and Figure 1).

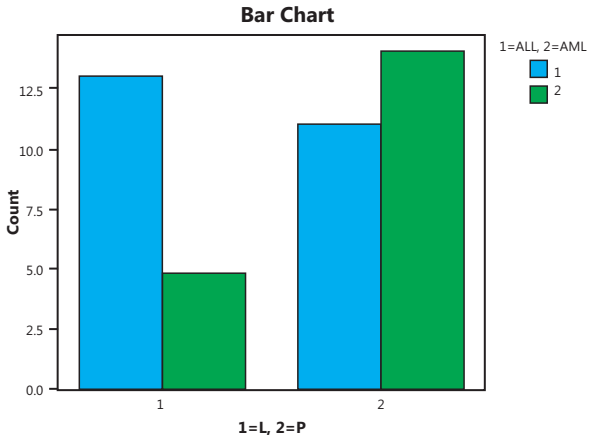


**Figure 1.** Graph of gender distribution in the lymphoid and myeloid lineage groups (L=Male, P=Female; lymphoid=blue, and myeloid=green)

This study involved 18 (41.9%) male and 25 (58.1%) female subjects. More male subjects were in the lymphoid lineage group than the myeloid lineage group, 13 (72%) vs. 5 (28%) subjects, respectively. Female subjects in the lymphoid lineage group were fewer than the myeloid lineage group, 11 (44%) vs. 14 (56%) subjects, respectively. There was no significant difference between the two groups.

The average Hb level, leukocyte count, and platelet count in all acute leukemia subjects were 9.05±1.69 g/dL, 27.60 (4.60-58.20) thousand/uL, and 39.00 (23-77) thousand/µL, respectively. There was no significant difference in the Hb levels of the lymphoid and myeloid lineage (9.33±1.84 g/dL vs.

**Table 2.** Basic characteristics of research subjects

| Variable | Acute leukemia, n (%) | | | p‡ |
|---|---|---|---|---|
| | Total | Lymphoid Lineage | Myeloid Lineage | |
| | 43 (100%) | 24 (55.8%) | 19 (44.2%) | |
| **Age** (years) | 25 (7-47) | 8 (2-43)$ | 40.9 ± 18.6* | **0.0001** |
| **Gender**, n (%)# | 43 (100) | 24 (55.8) | 19 (44.2) | 0.069 |
| Male# | 18 (41.9) | 13 (72) | 5 (28) | 0.059 |
| Female# | 25 (58.1) | 11 (44) | 14 (56) | 0.549 |
| **Hb** (g/dL)* | 9.05±1.69 | 9.33 ± 1.84* | 8.70 ± 1.44* | 0.232 |
| **AL** ($10^3$/uL) | 27.60 (4.60-58.20) | 14.4 (0.7-313.6)$ | 40.9 (1.4-198.7)$ | 0.175 |
| **AT** ($10^3$/uL) | 39.00 (23-77) | 40.5 (9-309)$ | 37 (5-229)$ | 0.922 |

$Data were not normally distributed, median (25th percentile-75th percentile), Mann-Whitney test. *Data were normally distributed, mean±SD, independent samples T-test

#Nominal data, Chi-Square test. ‡Significant if p<0.05, 95% confidence interval

Note: n= number, %= percentage, SD= Standard Deviation, Hb= hemoglobin, AL= leukocyte count, AT= platelet count, g= gram, dL= deciliter, uL= microliter

8.70±1.44 g/dL (p=0.232)). There was no significant difference in the total leukocyte count of both groups (14.4 (0.7-313.6) thousand/uL vs. 40.9 (1.4-198.7) thousand/uL, respectively) (p=0.175). There was no significant difference in the platelet counts of both groups (40.5 (9-309) thousand/uL vs. 37 (5-229) thousand/uL, p=0.922) (Table 2).

The average serum sodium level in acute leukemia subjects was 136 (132-140) mmol/L, and there was a significant difference between the lymphoid and myeloid lineage groups (134.38±4.75 mmol/L vs. 137.00 (121-143) mmol/L, respectively), with p=0.046 (Figure 2B). Serum potassium levels in acute leukemia were 3.42±0.68 mmol/L, but there was no significant difference between both groups (3.48±0.53 vs. 3.36±0.85 mmol/L, p=0.415) (Table 3).

Calcium ion levels in acute leukemia were 1.09 (1.01-1.13) mmol/L; there was no significant difference between lymphoid and myeloid lineage (1.09 (0.84-1.21) vs. 1.06±0.09 mmol/L, respectively, p=0.912). The mean PTHrp levels in acute leukemia subjects were 354.43 (84.75-934.95) pg/mL, and the mean PTHrp levels in the lymphoid and myeloid lineage groups were 396.48 (45.8-1116.70) pg/mL vs. 105.91 (20.77-1129.58) pg/mL, respectively. Still, no significant difference was found in both groups (p=0.293). Based on the ROC curve (Figure 3), the cut-off point for serum sodium levels to differentiate lymphoid and myeloid lineage was 135.5 mmol/L with the Area Under Curve (AUC) of 0.679, a sensitivity of 73.7%, and specificity of 67.7%. The myeloid lineage group in this study had a sodium level ≥ 135.5 mmol/L, and the lymphoid lineage group had a sodium level < 135.5 mmol/L.

The results of this study showed that the mean age was 25 (7-47) years, and there was a significant difference in age (p=0.0001) between the lymphoid lineage [8 (2-43) years] and myeloid lineage [40.9±18.6 years]. Guidelines from the College of American Pathologists and the American Society of

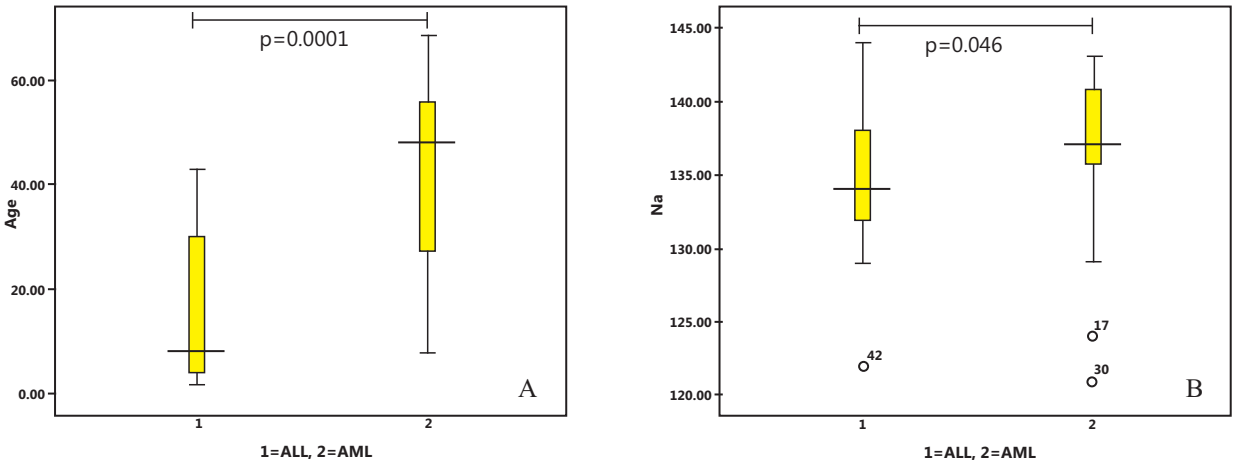


**Figure 2.** Graph of comparison of age (A) and serum sodium (Na) levels (B) in acute leukemia according to lymphoid lineage (1=ALL) and myeloid lineage (2=AML) groups

**Table 3.** Comparison of research variables

| Variable | Acute Leukemia | | | p‡ |
|---|---|---|---|---|
| | Total | Lymphoid Lineage | Myeloid Lineage | |
| **Sodium** (mmol/L) | 136 (132-140) | 134.38±4.75‡ | 137.00 (121-143)* | **0.046** |
| **Potassium** (mmol/L) | 3.42±0.68 | 3.48±0.53‡ | 3.36±0.85‡ | 0.415 |
| **Calcium ion** (mmol/L) | 1.09 (1.01-1.13) | 1.09 (0.84-1.21)* | 1.06±0.09‡ | 0.912 |
| **PTHrp** (pg/mL) | 354.43 (84.75-934.95) | 396.48 (45.8-1.116.70)* | 105.91 (20.77-1.129.58)* | 0.293 |

‡ Data were normally distributed, mean±SD, comparison of lymphoid and myeloid lineage was tested by independent samples T-test, significant if p<0.05.
*Data were not normally distributed, median ($25^{th}$-$75^{th}$ percentile), Mann-Whitney test, significant if p <0.05.
Note: PTHrp= Parathyroid hormone-related protein, mmol= millimoles, L= liters, pg= picogram, mL= milliliters

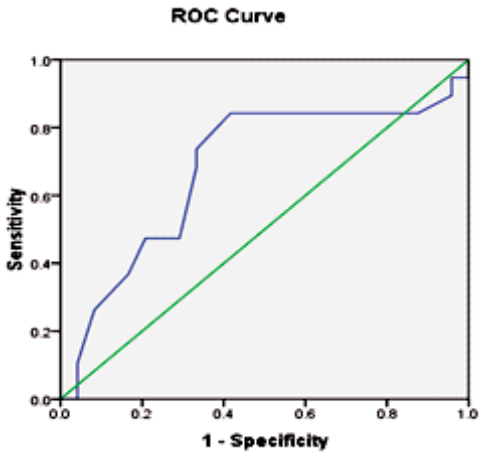


**Figure 3.** ROC curve with a cut-off point for serum sodium levels in acute leukemia

Hematology state that ALL children aged 1 to 9 years have better outcomes than those aged less than one year or more than ten years, whereas AML patients over 60 years of age have poorer outcomes compared to younger patients.[1]

This study found a higher number of male subjects in the lymphoid lineage group (13 or 72%) compared to the myeloid lineage group (5 or 28%); however, there was a higher number of female subjects in the myeloid lineage group (14 or 56%) compared to the lymphoid lineage group (11 or 44%) people, respectively. Arber *et al.* stated that gender is an important prognostic factor. In children with ALL, the male has a worse prognosis than the female; however, this difference is not clear in adult ALL, whereas in AML, the female has a worse prognosis than the male.[1]

Routine blood results of Hb, leukocyte count, and platelet count in this study generally indicated anemia (mean Hb 9.05±1.69 g/dL), leukocytosis [mean leukocyte count 7.60 (4.60-58.20) thousand/uL] and thrombocytopenia [mean platelet count 39.00 (23-77) thousand/uL]. The diagnosis of acute leukemia patients is initially based on abnormal routine blood results. Microscope examination of peripheral blood is also an initial screening for diagnosing acute leukemia patients, which generally detects anemia or thrombocytopenia.[1] Initial and ongoing evaluations for supportive care of patients with leukemia should include complete blood count, electrolytes, creatinine, liver enzymes, serum protein, uric acid, lactate dehydrogenase, coagulation studies, and blood cultures every 24 hours when febrile.[10]

Special bone marrow laboratory studies, which help detailed cell classification, include the following: immunophenotyping, cytogenetics, blood chemistry (electrolytes, Blood Urea Nitrogen (BUN), creatinine, calcium, phosphorous, uric acid, lactate dehydrogenase (LDH), and liver function tests), cerebrospinal fluid (CSF), coagulation profile, cardiac function, and infectious disease profile.[11] electrolyte balance disorders, such as hypokalemia, are common in acute leukemia patients.[12] The mechanism of hypokalemia in AML (especially in subtypes M4 and M5) is through proximal tubular injury by lysozyme in urine. Another case report mentions high levels of renal-independent renin secretion from AML blast cells induce secondary hyperaldosteronism and hypokalemia; this needs to be differentiated from pseudo-hypokalemia due to potassium uptake due to the high number of leukocyte cells. Myelopoietic growth factor therapy has also stimulated intra-cellular shifting of potassium due to rapid cell proliferation, resulting in hypokalemia.[2]

Some cases of acute leukemia can be found with severe hyponatremia.[12] This study found a significant difference in mean serum sodium levels between the two acute leukemia lineage groups but not in the potassium, calcium ion, and PTHrp levels. The average serum sodium level in all study subjects was 136 (132-140) mmol/L, while in the lymphoid and myeloid lineage groups were 134.38±4.75 mmol/L vs. 137.00 (121-143) mmol/L (p=0.046). The cut-off point for serum sodium levels in this study was 135.5 mmol/L with an AUC of 0.679, sensitivity of 73.7%, and specificity of 67.7%.

This study could not clinically differentiate myeloid and lymphoid acute leukemias solely based on the cut-off of sodium levels of 135.5 mmol/L because the bar charts of sodium levels between myeloid and lymphoid subjects were closely overlapping. In contrast, this study's cut-off point of 135.5 mmol/L was within the normal reference value of sodium (135-145 mmol/L). Because sodium electrolyte levels are influenced by many factors such as renal function, intake, medication, and disease, a further study with many samples from different centers and another parameter with a model multivariate study was considered necessary.

Hyponatremia (plasma sodium level <135 mmol/L) is a common condition of fluid balance disturbances, often challenging the diagnosis and appropriate therapy. Hyponatremia is not a disease but a pathophysiological process indicating a disturbance of fluid homeostasis. Hyponatremia in acute leukemia may be caused by cytotoxic therapy, cerebral salt-wasting syndrome (CSW), and others. The pathophysiology of CSW is not fully understood, but it is suspected that there is impaired sodium

absorption in the nephrons of the kidney's proximal tubule. The CSW syndrome is Reduced intravascular volume due to natriuresis, Hyponatremia, Diuresis due to excess urine volume, increased urinary sodium excretion, and normal or increased urinary osmolality.[13]

Tumor cells induce hypercalcemia directly by invading bone or by producing factors that locally or systemically activate osteoclasts. Several factors that cause hypercalcemia are Tumor Necrosis Factor (TNF)-α, TNF-β, Interleukin (IL)-1α, IL-6, IL-1β, Transforming Growth Factor (TGF)-α, TGF-β, ectopic PTH, PTHrP, 1,25 dihydroxy vitamin D, prostaglandin (PG)-E1, PG-E2, receptor activator of nuclear factor κB, ligand/osteoprotegerin system (RANKL), Macrophage Colony-Stimulating Factor (M-CSF), Macrophage Inflammatory Protein (MIP)-1α, and lymphotoxin.[3]

Parathyroid hormone is a protein released by the parathyroid glands with 84 amino acids, which plays an essential role in calcium regulation and is not directly affected by intestinal calcium absorption by regulating the synthesis of 1,25-dihydroxy vitamin D.[14] Decreased calcium ions promote PTH release, which maintains calcium homeostasis by increasing bone mineral breakdown, thereby releasing calcium and phosphorus; Increasing calcium reabsorption and phosphorus excretion; Increasing gastrointestinal absorption of both phosphorus and calcium indirectly through the effect of synthesis of 1,25 (OH) 2D (calcitriol).[15]

This study obtained an average PTHrp level of 354.43 (84.75-934.95) pg/mL in acute leukemia subjects. The lymphoid and myeloid lineage groups got PTHrp levels of 396.48 (45.8-1,116.70) pg/mL vs. 105.91 (20.77-1,129.58) pg/mL, respectively, but no significant difference was found in both group (p=0.293). No differences in PTHrp levels between lymphoid and myeloid lineages might be because the population in this study were new leukemia patients, and there was no therapy or chemotherapy yet.

It is estimated that hypercalcemia occurs in 10% of malignancies. Malignancy-associated hypercalcemia (MAH) may appear with or without increased production of PTHrP. Immunoradiometric tests for PTHrP show that 20-60% of patients had hematological malignancies and hypercalcemia, and 50-90% had solid tumors and hypercalcemia, which have increased circulating PTHrP.[16] The normal value of PTH was 9.2-44.6 pg/mL.[17] Hematological malignancies that can cause hypercalcemia include lymphoblastic leukemia, chronic myeloid, adult T-cell lymphoma (ATL), non-Hodgkin lymphoma, and multiple myeloma.[16]

An observational analysis and cross-sectional study remained the limitations of this study. In addition, this study was only conducted on acute leukemia subjects to analyze PTHrp and serum electrolytes without using a control group. Further research was needed to confirm the presence of both primary and secondary hyperparathyroidism in acute leukemia patients. A prospective cohort, retrospective cohort, or case-control approach with subjects other than acute leukemia, such as chronic leukemia (CLL or CML), and other variables such as electrolyte chloride, magnesium, and phosphate were also needed. Therefore, an electrolyte balance disorder in leukemia research subjects can certainly be confirmed.

## CONCLUSIONS AND SUGGESTIONS

There were no significant differences in PTHrp levels and serum electrolytes (potassium, calcium ions) in patients with acute myeloid and lymphoid leukemia lineage, but there were significant differences in serum sodium electrolyte levels in patients with acute lymphoid and myeloid lineage.

Further research was needed using a prospective cohort, retrospective cohort, or case-control approach with chronic leukemia subjects as well as chloride, magnesium, and phosphate electrolyte variables to confirm electrolyte balance disorders in leukemia.

## ACKNOWLEDGMENTS

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