Evaluation of circulating renin-angiotensin system components in pediatric patients with acute leukemia: a pilot study

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Research Article

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Abstract

Introduction: Acute leukemia (AL) is the most common cancer of childhood. Recently, an important advance in the survival rate of these patients. The objective of this study was to assess whether there is an association between the blood levels of Renin Angiotensin System (RAS) molecules in children with acute AL and disease presentation and evolution in pediatric patients.

Materials and Methods: This is a cross-sectional study carried out in a group of pediatric patients with AL. We measured blood levels of Angiotensin II (Ang II) and Angiotensin-(1-7) [Ang-(1-7)] by enzyme immunoassay. The Ang-(1-7)/Ang II ratio was calculated as a parameter of the balance between the alternative and classical axes of the RAS.

Results: Eleven patients with AL and 20 healthy controls matched by sex and age were included. Patients with AL had significantly higher levels of both peptides when compared with healthy controls (p < 0.05). However, no significant difference was found in the Ang-(1-7)/Ang II ratio between the two groups. A strong and positive correlation was detected between Ang II and Ang-(1-7) levels in patients with AL (r = 0.853; p < 0.0001). There was no significant difference between the levels of Ang II and Ang-(1-7), as well as the Ang-(1-7)/Ang II ratio, the type of AL and clinical outcomes.

Conclusion: Both Ang-(1-7) and Ang II seem to be involved in the physiopathology of AL and other molecules of the RAS could be potentially explored for the development of new therapeutic options for AL.

Introduction

Acute leukemias represent approximately 30% of childhood neoplasms and are the most common cancer among children [1]. The pathophysiology starts with an alteration in the clonal proliferation of cells of lymphocytic or myelocytic lineage, generating an accumulation of cells in the marrow at early stages of maturation. These cells are called blasts and accumulate in the bone marrow, replacing the population of normal cells with altered cells. Approximately 80% of childhood acute leukemias are represented by lymphocytic lineage alterations (Acute Lymphoblastic Leukemia, or ALL), while 15% are myelocytic lineage alterations (Acute Myeloid Leukemia, or AML). A small percentage of these leukemias may present as biphenotypic or undergo a change in classification during treatment. Childhood neoplasms are characterized by having short latency periods, more aggressive presentation, and accelerated growth if compared with the disease in adults. On the other hand, they respond better to treatment and have a good prognosis in most cases [2].

The treatment consists of antineoplastic chemotherapeutic agents, which kill cancer cells through their systemic action. These chemotherapeutic agents have low specificity, acting on neoplastic and normal cells that have high mitotic activity and short cell cycle, which implies their high toxicity. Approximately 1–2% of children with ALL die before reaching remission, and another 1–2% die from the toxic effects of the treatment during remission [3].

In this scenario, a series of studies have emerged in recent decades [4–6] that aimed at developing treatment regimens for acute childhood leukemia that maintain the efficacy and high cure rates of current regimens, but offer less toxicity and lower risk of short- and long-term side effects. The knowledge about the pathophysiology of the disease, the genetic and molecular alterations, and the mechanisms of chemotherapy resistance made possible the recent development of numerous drugs that target the main molecular pathways related to the development of leukemia, growth, and cell proliferation [7]. Among the endogenous molecules, still poorly studied, which could possibly act directly on the proliferation of leukemic neoplastic cells are the Renin Angiotensin System (RAS) components, such as Angiotensin-(1–7) [Ang-(1–7)] and Angiotensin II (Ang II).

Ang-(1–7) is an endogenous heptapeptide molecule of the RAS responsible for coordinating biological responses by activating a single receptor, the Mas receptor. The importance of investigating the role of Ang-(1–7) in hematological
neoplasms is based on the ability of this heptapeptide to inhibit the growth of several cell lines [4] and to accelerate bone marrow recovery after periods of aplasia resulting from chemotherapy [5].

Previous studies have linked Ang-(1–7) to growth inhibition and reduced proliferation of human cancer cells and in xenographic tumors, through several actions. Ang-(1–7) reduces angiogenesis, cancer-associated fibrosis, osteoclastogenesis, tumor-induced inflammation, and metastases [4, 6]. A series of studies [8–10] showed that Ang-(1–7) inhibits the growth of different cancer cells by reducing the activity of cyclooxygenase 2 (COX-2) and inflammatory prostaglandins. The inhibition of COX-2 [11] directly reduces the formation of prostaglandin E2 (PGE-2) in the tumor tissue, preventing the stimulation of VEGF, responsible for inducing angiogenesis and indirectly stimulating the growth and expansion of the neoplastic cell. Studies with lung and prostate cancer cells [6, 12] demonstrated an inhibition of the growth of these cells associated with a reduction in the expression of Ki67, a specific cell proliferation marker, when incubated with Ang-(1–7). Another study [5] showed that Ang-(1–7) accelerates hematopoietic recovery in peripheral blood and bone marrow after chemotherapy. The action of the heptapeptide seems to occur in synergy with previously existing multi-lineage growth factors, increasing the proliferative effect on myeloid, megakaryocytic, erythroid and common myeloid cell progenitors [5].

Considering these studies, it is likely that Ang-(1–7) can also play an important role in the control and evolution of acute leukemias in children [4]. Thus, the objective of the present study was to evaluate, through the measurement of circulating Ang-(1–7) and Ang II levels, in pediatric patients with acute leukemia, whether there is any association between the concentrations of these molecules and the clinical characteristics of the disease, as well as its response to chemotherapy and evolution.

**Materials And Methods**

**Study design and location**

This is a cross-sectional study whose primary outcome of interest was the plasma measurement of Ang II and Ang-(1–7) in pediatric patients diagnosed with acute leukemia and followed-up at the Pediatric Hematology Service of Hospital das Clínicas da UFMG (HC-UFMG). The control group consisted of healthy pediatric patients regularly followed up at the Pediatric outpatient service of the HC-UFMG, matched by sex and age.

**Ethical considerations**

The project was approved by the Ethics and Research Committees (COEP) of the Federal University of Minas Gerais under the protocol COEP 5.192.807. The research team invited patients to participate in the study. Those who agreed were included in the study by signing the Free and Informed Consent Term (FICT) and Assent Term. All study information was kept confidential to preserve the identity of patients, and all biological material collected was used only for research.

**Study population**

The study was carried out in pediatric patients aged between 6 months and 16 years at diagnosis, in regular follow-up at the Pediatric Hematology Outpatient Clinic at UFMG. The study included all patients with a recent diagnosis of acute leukemia admitted to the service between July 2021 and January 2022, as well as patients with acute leukemia who were already being followed up in this service since 2018 and agreed to participate in the research. The main criteria for selection were patients who had a diagnosis of acute leukemia confirmed by immunophenotyping, as well as healthy controls matched by sex and age.

Ang II and Ang-(1–7) were measured in peripheral blood samples from patients and healthy controls.

**Inclusion criteria**
The criteria adopted for the inclusion of participants in this study were: (i) pediatric patients diagnosed with acute leukemia, aged between 6 months and 16 years, regularly followed up at the Pediatric Hematology service of HC-UFMG, (ii) confirmed diagnosis of acute leukemia through immunophenotyping and (iii) consent to participate in the study by signing the consent form and assent term.

**Exclusion criteria**

The exclusion criteria adopted in this study were: (i) patients diagnosed with chronic leukemias or other medullary alterations other than acute leukemias, (ii) patients or family members who did not accept to participate in the study and (iii) patients over 16 years of age at diagnosis.

**Angiotensin II and Angiotensin-(1–7) blood levels**

Peripheral venous blood was collected from all participants. The samples were placed in vacuum tubes with heparin and centrifuged twice at 1000xg for 20 minutes at 4°C. The supernatant was then collected and stored at -70°C until processing. Quantitative sandwich single antigen enzyme immunoassay (ELISA) kits were used to measure plasma levels of Ang-(1–7) (catalog #MBS084052) and Ang II (#MBS028394), following the manufacturer's instructions (MyBioSource, 22 San Diego, CA, United States). The concentration measurement was in pg/mL and the reported sensitivity for both analytes is 2.0 pg/ml. The samples were analyzed in a single assay to avoid the influence of inter-assay variability. The intra-assay variability was less than 3%. In addition to the Ang-(1–7) and Ang II levels measured, the Ang-(1–7)/Ang II ratio was calculated as a parameter for the balance between the alternative and classical axes of the RAS.

**Clinical variables of patients**

To assess whether there was any association between Ang II and Ang-(1–7) levels with the clinical characteristics of patients, a retrospective analysis of medical records was performed. The following variables were included: ALL subtype, karyotype, molecular biology, the therapeutic protocol used, presence of hyperleukocytosis at diagnosis, the occurrence of complications, and outcomes. The patients' division was according to the presence of lymphoblasts at diagnosis in the central nervous system (CNS) into three groups: CNS1 - the absence of blasts; CNS2 – leukocyte count < 5/µl with the presence of blasts and CNS3 – leukocyte count ≥ 5/µl with the presence of blasts [13].

**Statistical analysis**

Statistical analyzes were performed using GraphPad Prism 8.4.3 software (GraphPad Software, San Diego, CA, United States). To assess the normal distribution of the data, we visually inspect the distribution of each of the continuous variables and submit them to the Shapiro-Wilk test. About continuous variables, the two groups (Acute Leukemia and control) were compared using the Mann-Whitney U test or the unpaired Student's T-Test, according to their distribution. Fisher's exact test and the chi-square test were used to compare categorical (binary) variables between groups. Correlations between variables were calculated using the Spearman or Pearson coefficient, depending on the distribution. When the study sample was subdivided into three categories, comparisons were made by analysis of variance (ANOVA) or by the Kruskal Wallis test.

**Results**

**Clinical data**

Eleven patients with acute leukemia and 20 healthy controls matched by sex and age were included. In the group of patients, 8 (72.7%) were male. The age of the participants ranged from 11 months to 13 years (7.51 ± 4.74 years of age). The characteristics of patients and controls can be seen in Table 1. Of the 11 patients diagnosed with AL, 8 (72.7%) had B ALL, 2 (18.2%) had T ALL, and only 1 (9.1%) had AML. Of the 8 patients with ALL B, 2 (25%) were classified as low risk, 3 (37.5%) as intermediate risk and 3 (37.5%) as high risk. Regarding the classification of CNS involvement at diagnosis,
the patients followed up, 7 (63.6%) were classified as CNS1, 2 (18.2%) as CNS2 and 2 (18.2%) as CNS3. Only 2 (18.1%) patients had hypercellularity at diagnosis. The most used therapeutic regimen was BFM 2009 (72.7%), followed by Nopho03 (9.1%) and GBTLI 2009 (9.1%), and in only one (9.1%) patient, two different protocols were performed, due to the change in the classification of the disease (Nopho03 and GBTLI). Regarding the clinical outcome, 10 (90.9%) patients were in morphological remission and only 1 (9.1%) died during disease induction treatment. Of the patients in remission, 8 (72.7%) remained under chemotherapy treatment according to the protocol, 1 (9.1%) was referred for bone marrow transplantation at another institution and 2 (18.2%) had chemotherapy suspended due to discharge, toxicity, and associated morbidity, being under regular follow-up at the outpatient clinic, with periodic reassessment of disease activity. The individual characteristics of each acute leukemia patient can be seen in Table 2.

Table 1
Comparison between patients with acute leukemia (AL) and healthy controls.

<table>
<thead>
<tr>
<th>Variables</th>
<th>AL (n = 11)</th>
<th>Controls (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M / F)</td>
<td>8 / 3</td>
<td>12 / 8</td>
<td>0.698</td>
</tr>
<tr>
<td>Age (years)</td>
<td>7.51 ± 4.74</td>
<td>8.25 ± 3.72</td>
<td>0.634</td>
</tr>
<tr>
<td>Ang-(1–7) (pg/mL)</td>
<td>232.1 ± 60.37</td>
<td>93.91 ± 33.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ang II (pg/mL)</td>
<td>289.3 ± 101.1</td>
<td>115.5 ± 49.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ang-(1–7)/AngII Ratio</td>
<td>0.86 ± 0.24</td>
<td>0.93 ± 0.44</td>
<td>0.984</td>
</tr>
</tbody>
</table>

Ang-(1–7): Angiotensin-(1–7); Ang II: Angiotensin II; F: female; M: male. *Mann Whitney U-Test or Unpaired Student’s T-Test. Values in mean or median ± standard deviation.
Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>CNS</th>
<th>Karyotype</th>
<th>Treatment protocol</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.67</td>
<td>F</td>
<td>B ALL IR</td>
<td>CNS2</td>
<td>46, XX,i(7)(q10)[05]/46,XX[11]</td>
<td>BFM2009</td>
<td>Remission</td>
</tr>
<tr>
<td>2</td>
<td>12.00</td>
<td>F</td>
<td>ALL B HR</td>
<td>CNS1</td>
<td>46, XY</td>
<td>BFM 2009</td>
<td>Remission</td>
</tr>
<tr>
<td>3</td>
<td>5.58</td>
<td>M</td>
<td>ALL pro-B MLL+/ Switch hyperleukocytic</td>
<td>CNS1</td>
<td>46,XX,t(4;11)(q21;q23)/46,XX</td>
<td>GBTLI LLA BFM 2009/Nopho93</td>
<td>BMT</td>
</tr>
<tr>
<td>4</td>
<td>1.92</td>
<td>M</td>
<td>ALL early T</td>
<td>CNS1</td>
<td>45,XY,8[03]/46,XY[12]</td>
<td>BFM 2009</td>
<td>Deceased</td>
</tr>
<tr>
<td>5</td>
<td>8.00</td>
<td>M</td>
<td>ALL pre-B IR</td>
<td>CNS3</td>
<td>NOMA</td>
<td>BFM2009</td>
<td>Remission</td>
</tr>
<tr>
<td>6</td>
<td>0.92</td>
<td>F</td>
<td>AML M7 + trisomy 21</td>
<td>CNS1</td>
<td>47,XY,+21[12]/48,XY,+8,+21[08]</td>
<td>Nopho03</td>
<td>Remission</td>
</tr>
<tr>
<td>7</td>
<td>4.42</td>
<td>M</td>
<td>ALL pre-B ph + HR</td>
<td>CNS3</td>
<td>NOMA</td>
<td>BFM2009</td>
<td>Remission</td>
</tr>
<tr>
<td>8</td>
<td>5.92</td>
<td>M</td>
<td>ALL T HR</td>
<td>CNS2</td>
<td>NOMA</td>
<td>GBTLI 2009</td>
<td>Remission</td>
</tr>
<tr>
<td>9</td>
<td>6.00</td>
<td>M</td>
<td>ALL B LR</td>
<td>CNS1</td>
<td>NOMA</td>
<td>BFM2009</td>
<td>Remission</td>
</tr>
<tr>
<td>10</td>
<td>16.50</td>
<td>M</td>
<td>ALL B LR</td>
<td>CNS1</td>
<td>NOMA</td>
<td>BFM2009</td>
<td>Remission</td>
</tr>
<tr>
<td>11</td>
<td>8.33</td>
<td>F</td>
<td>ALL B IR</td>
<td>CNS1</td>
<td>NOMA</td>
<td>BFM2009</td>
<td>Remission</td>
</tr>
</tbody>
</table>

ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; F: female; NOMA: not enough metaphyses were obtained for karyotype analysis at diagnosis; M: male; BMT: bone marrow transplantation; LR: low risk; IR: intermediate risk; HR: high risk; CNS: central nervous system.

Angiotensin II and Angiotensin-(1–7) in patients with acute leukemia

Blood levels of Ang II and Ang-(1–7) were measured in patients with acute leukemia and healthy controls. It was noted that patients with acute leukemia had significantly higher levels of both peptides when compared to healthy controls (Table 1, Figs. 1A and 1B). However, no significant difference was found in the Ang-(1–7)/Ang II ratio between the two groups (Table 1, Fig. 1C). A strong and positive correlation was detected between Ang II and Ang-(1–7) levels in patients with acute leukemia (r = 0.853; p < 0.0001) (Fig. 2A). A similar result was not found in healthy controls (Fig. 2B).

Angiotensin II and Angiotensin-(1–7) and characteristics and outcomes of patients with acute leukemia

Analyzes were performed regarding the levels of the two peptides and different clinical characteristics of patients with acute leukemia and healthy controls. As expected, no differences were found in the levels of Ang II and Ang-(1–7) according to the sex of patients with acute leukemia and healthy controls. However, it was noted that there was a positive correlation between age and Ang II levels in healthy controls (r = 0.630; p = 0.002), a result not found in patients with acute leukemia (Table 3). Furthermore, it was noticed that only healthy controls had a negative correlation between the Ang-(1–7)/Ang II ratio and age (r = -0.580; p = 0.073). There was no significant difference between the levels of Ang II and Ang-(1–7), as well as the Ang-(1–7)/Ang II ratio, between the different levels of CNS involvement (p > 0.05), as well as among patients with ALL B, ALL T and AML (p > 0.05). Similarly, the presence of hypercellularity was not associated with distinct levels of the peptides or their relationship (p > 0.05). Treatment protocols and karyotype were not associated with higher or lower levels of Ang II and Ang-(1–7) (p > 0.05).
Table 3
Correlations between levels of angiotensin II (Ang II), angiotensin-(1–7) [Ang-(1–7)] and Ang-(1–7)/Ang II ratio in patients with acute leukemia (AL) and healthy controls.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rho (r)* coefficient</th>
<th>CI95%</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang-(1–7) (pg/mL)</td>
<td>-0.081</td>
<td>-0.661–0.559</td>
<td>0.817</td>
</tr>
<tr>
<td>Ang II (pg/mL)</td>
<td>-0.036</td>
<td>-0.6350–0.5896</td>
<td>0.924</td>
</tr>
<tr>
<td>Ang-(1–7)/AngII ratio</td>
<td>0.06364</td>
<td>-0.571–0.651</td>
<td>0.8603</td>
</tr>
<tr>
<td>Controls (n = 20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang-(1–7) (pg/mL)</td>
<td>-0.130</td>
<td>-0.551–0.343</td>
<td>0.582</td>
</tr>
<tr>
<td>Ang II (pg/mL)</td>
<td>0.630</td>
<td>0.248–0.843</td>
<td>0.002</td>
</tr>
<tr>
<td>Ang-(1–7)/AngII ratio</td>
<td>-0.580</td>
<td>-0.818 – -0.171</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Ang-(1–7): Angiotensin-(1–7); Ang II: Angiotensin II; 95%CI: Confidence Interval of 95%. *Spearman’s coefficient.

Discussion
To our knowledge, this is the first study that evaluated the plasma levels of RAS components in pediatric patients with acute leukemia. We found that patients with acute leukemia presented considerably higher levels of Ang II and Ang (1–7) when compared to healthy controls, though it was not found a significant difference in the Ang II/Ang (1–7) ratio between both groups. We found a positive correlation between age and Ang II levels in healthy controls, which was not encountered in patients with acute leukemia. This finding is consistent with one described in a previous study that demonstrated an increase in peptides related to the classical RAS axis with increasing age [14]. It was also noticed that healthy controls had a negative correlation between the Ang-(1–7)/Ang II ratio and age, corroborating data previously described in the literature [15]. The increase in the concentration of Ang II in leukemia patients compared to the control group is compatible with another previous study that associated high levels of ACE activity in the bone marrow with an excessive and disordered proliferation of hematopoietic progenitors and stem cells pluripotent hematopoietic cells [16]. These findings also reinforce the hypothesis that there is an alteration in the homeostasis and functioning of the RAS in patients with leukemia.

Acute leukemias are the neoplastic group more common in childhood and, despite currently presenting a survival rate of about 80% [1], the disease and the morbidity associated with treatment lead to a great impact on these patients’ life quality, in short, medium, and long terms. Positive response to treatment and increased survival rate in the last decades are due to more physiopathology as well as to genetic and molecular mechanisms understanding in their different presentation forms. This knowledge allowed, in the last years, the development of numerous drugs that target molecular pathways associated with the emergence, proliferation, and maintenance of leukemic clones. Among the molecules that could potentially act directly in each of these leukemic clone cells growing and maintaining stages, emerge Ang-(1–7).

Ang-(1–7) is a RAS endogenous heptapeptide hormone responsible for coordinating the biological response through activation of only one receptor, the Mas receptor, which can reach specific targets when utilized as a therapeutic agent. Previous studies [4, 6] related Ang-(1–7) to inhibition of growth and reduction of carcinogenic human cells and xenographic tumor proliferation by diverse mechanisms, including angiogenesis and inflammation reduction induced by the tumor and its metastasis. Another study [5] showed that Ang-(1–7) accelerates hematopoietic recovery in peripheral blood and bone marrow after chemotherapy, synergistically acting with multi-lineage growth factors that existed previously and incrementing the proliferative effect in medullary progenitors.
The absence of a positive correlation between age and Ang II levels in patients with leukemia reinforces the hypothesis that the alterations found in the concentrations of peptides in these patients are attributable to the underlying disease. The increase in Ang II was expected among these patients, considering its pro-tumorigenic and pro-inflammatory actions already demonstrated *in vitro* and *in vivo* [17, 18]. The equivalent and proportional increase in the concentration of both peptides in the patients suggests an augmentation in Ang-(1–7) due to greater conversion of Ang II into Ang-(1–7) by the action of angiotensin converting enzyme 2 (ACE2) [19].

On the other hand, there was no significant difference between the levels of Ang II and Ang-(1–7), as well as the Ang-(1–7)/Ang II ratio, between the different levels of involvement of the CNS, which may suggest a low involvement of these molecules in the process of CNS infiltration of these patients. These findings differ from those reported in previous studies in which the action of these molecules was directly related to the capacity of solid tumors to proliferate and generate metastases [20], as well as the important biological role of Ang - (1–7) in brain tissue [13]. It should be noted that the reduced size of our sample of pediatric patients with acute leukemia may have compromised the analysis.

There was also no significant difference between the levels of Ang II and Ang-(1–7) between patients with ALL B, ALL T, and AML, which suggests that the mechanisms of action and functioning of the RAS in hematological neoplasms occur in a similar in the different types of leukemia presentation. Also in this case, the small sample size may have prevented the detection of significant differences between the subgroups. The presence of hypercellularity at diagnosis was not associated with distinct levels of the evaluated peptides or their relationship. The treatment protocols and karyotype were not associated with higher or lower levels of Ang II and Ang-(1–7). Thus, our study did not allow, from this perspective, to establish a relationship between initial disease risk stratification and plasma levels of the peptides.

The present study had some limitations, including small sample size, due to the specific inclusion criteria for participation. For a better understanding of the action of RAS peptides in acute leukemias, a long-term follow-up would be important in many patients, as well as the possibility of measuring other RAS molecules. In this case, the ACE2 dosage or the measurement of enzymatic activity, for example, could reinforce the suggested hypothesis of an increase in Ang-(1–7) secondary to increased degradation of Ang II by ACE2 in these patients. Furthermore, the possibility of measuring the peptides in the cerebrospinal fluid of patients could elucidate their role in CNS infiltration by the underlying disease.

In conclusion, we found preliminary evidence for a role of Ang II and Ang-(1–7) in acute leukemias of pediatric patients. However, additional studies are needed to establish an association between the disease outcome and RAS molecules.

**Declarations**

**Conflicts of interest:** The authors declare no conflicts of interest.

**Authors contribution:** ALBP evaluated patients and controls, collected blood samples, helped in the measurements, and wrote the first draft, PASVC performed the measurements, data analysis, and helped in writing the first draft, RGS and JPFR helped in patients evaluation and blood samples collections, revised the medical records and helped in writing the first draft, ACSS made general supervision, revised and submitted the manuscript, which is approved by all authors.

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**References**


Figures
Dosage of Angiotensin II (Ang II) and Angiotensin-(1-7) [Ang-(1-7)]. (A) Patients with acute leukemia (AL) have higher levels of Ang II (pg/mL) and (B) Ang-(1-7) when compared to healthy controls. (C) There was no significant difference between the Ang II/Ang-(1-7) ratio between the two groups. ****p < 0.0001.
Figure 2

Correlation of Angiotensin II and Angiotensin-1(1-7) levels in the group of (A) patients with acute leukemia (AL) and (B) healthy controls. A positive correlation between the levels of both molecules was noted only in patients with LA.