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Lysophosphatidylcholine Acyltransferase 1 (LPCAT1): A Predictor of Acute Leukemia Prognosis

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Abstract
Background: *Lysophosphatidylcholine acyltransferases 1 (LPCAT1)* overexpression and prognostic significance have been shown in various human solid cancers. However, the role of *LPCAT1* in hematological malignancies has yet to be extensively explored. The present study primarily aimed to explore the *LPCAT1* expression and prognostic significance in patients diagnosed with acute leukemia.
Method: This cross-sectional study was conducted on 140 acute leukemia patients (70 AML and 70 ALL patients) and 70 healthy controls. *LPCAT1* expression levels and survival rate were evaluated. Patients' clinical data were extracted from their archived medical records, and the association between *LPCAT1* expression and clinical data was determined. Statistical analyses were conducted using IBM SPSS version 21 and GraphPad Prism version 9.5.0.
Results: The findings of this study indicated that *LPCAT1* expression levels were significantly higher in AML and ALL cases as compared with the healthy controls (P = 0.038 and 0.032, respectively). Kaplan-Meier analysis demonstrated that *LPCAT1* overexpression was correlated with shorter overall survival in both AML and ALL patients (P = 0.013 and 0.019, respectively). Moreover, multivariate Cox regression analysis revealed that *LPCAT1* overexpression was an unfavorable prognostic factor associated with shorter overall survival in patients with AML (P = 0.02) and ALL (P = 0.04). There was no significant difference regarding clinical parameters between $LPCAT1^{high}$ and $LPCAT1^{low}$ patients ($P > 0.05$).

Conclusion: *LPCAT1* overexpression is associated with poor prognosis in newly diagnosed patients with AML and ALL. As a result, further attention should be paid when considering treatment options for these patients.

Keywords: *LPCAT1*, Acute myeloid leukemia, Acute lymphoblastic leukemia, Gene expression, Prognosis

Introduction

Acute myeloid leukemia (AML), the major form of leukemia in adults and newborns, is characterized by the aberrant proliferation of immature myeloid precursors that disrupt normal hematopoiesis.[1] However, acute lymphoblastic leukemia (ALL) arises from the rapid growth of immature lymphoid cells in the bone marrow. It is the most prevalent type of acute leukemia in school-aged children, accounting for 75%–80% of cases. Also, there is a rise in ALL occurrences in cases around the fifth decade of life.[2] While acute leukemias typically exhibit an initial response to chemotherapy, they show a poor prognosis if not promptly treated.[3] Genetic alterations, such as mutations, chromosomal rearrangements, and aberrant gene expression, influence the pathogenesis and prognosis of AML and ALL.[2, 4]

Significant alterations in cellular metabolic pathways have been reported in leukemia. As a result, studying the expression levels of metabolism-related genes helps us identify novel therapeutic targets and potential prognostic markers for leukemia.[5] Although several prognostic factors have been identified in acute leukemia, there is still a crucial need to identify more robust predictors.

Lipids are essential components of cell membranes that play crucial roles in diverse cellular metabolic pathways, including energy production, molecular signaling, and metabolism. Dysregulation in lipid metabolism is associated with cancer progression.[6] Phosphatidylcholine (PC) is the predominant phospholipid class in cell membranes.[7] The *lysophosphatidylcholine acyltransferase (LPCAT)* family comprises a group of cytosolic enzymes that play essential roles in converting *lysophosphatidylcholine (LPC)* to PC. *Lysophosphatidylcholine acyltransferases 1 (LPCAT1)* is one of the four isoforms of this enzyme family.[8] Several studies have shown that *LPCAT1* expression is altered in various human malignancies, including hepatocellular carcinoma, prostate cancer, breast cancer, colorectal cancer, renal clear cell carcinoma, gastric cancer, and lung adenocarcinoma. Additionally, *LPCAT1* overexpression is linked with unfavorable prognosis in some of these cancers.[9-16]

Limited research has focused on the prognostic significance of *LPCAT1* in hematologic malignancies, with only one study exploring its implications in AML[17] and there have been no studies exploring its significance in (ALL). Therefore, the present study aimed to assess the association between *LPCAT1* expression levels and prognosis in patients with AML and ALL.

Materials and Methods

Patients' characteristics

This cross-sectional study was conducted at the Cancer Molecular Pathology Research Center, Ghaem Hospital of Mashhad University of Medical Sciences (MUMS), Mashhad, Iran. A total number of 140 newly diagnosed patients were randomly selected, including 70 AML and 70 ALL patients. All patients were referred to the Cancer Molecular Pathology Research Center between November 2017 and December 2019. AML and ALL diagnoses were confirmed by two pathologists following the

French-American-British (FAB) criteria and the World Health Organization (WHO) classification in terms of morphological, cytochemical, immunophenotyping, and molecular evaluations. In addition, 70 healthy controls with no history of cancer were included in the study, consisting of 40 healthy adults as the control group for AML patients and 30 healthy pediatric individuals as the control group for ALL patients. The controls were matched with patients by their age and gender. The sample size was determined based on a previous study by Wang et al. study.[17]

Ethics approval

This study received approval from the Ethics Committee of MUMS (Ethics code: IR.MUMS.MEDICAL.REC.1401.125), and all participants provided informed consent either personally or through their parents in the case of individuals under 18 years of age.

RNA isolation and cDNA synthesis

Peripheral blood mononuclear cells (PBMCs) were isolated via Ficoll gradient centrifugation. Total RNA was extracted from PB samples using the RNeasy Kit (AddBio, Korea Cat. No. 10119) according to the manufacturer's instructions. The concentration and purity of RNA were evaluated by measuring the absorbance at 260:280 nm using the Nanodrop 2000 Spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA). In addition, RNA integrity was verified by electrophoresis on a 1.5% agarose gel by adding 2µl of RNA to visualize the 18S and 28S subunits of ribosomal RNA. Samples with inadequate quality and low RNA concentrations were excluded from the study. cDNA synthesis was conducted using cDNA Synthesis Kit (AddBio, Korea Cat. No. 22701) according to the provided protocol: 5µl of RNA were mixed with 10 µl of 2x Reaction Buffer, 2 µl dNTP, 2 µl oligo dt (10x random hexamer), and 1 µl Enzyme solution.

Real-Time quantitative polymerase chain reaction (RT-qPCR) for LPCAT1 expression

LPCAT1 gene expression was determined by real-time quantitative PCR using SYBR Green Master Mix (AddBio, Korea Cat. No. 70205) on an ABI StepOne system (Applied Biosystems, Foster City, CA, USA). PCR cycling conditions included initial denaturation at 95Cº for 10 minutes, followed by 40 cycles at 95Cº for 15 seconds and 60Cº for 60 seconds. The melt curve was set at 60Cº for 10 seconds and 95Cº for 10 seconds. RT-qPCR efficiency was determined using the standard curve slope by preparing a dilution series (5-fold dilutions) of cDNA samples. Glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) was used as the reference gene. Primer sequences for *LPCAT1* and *GAPDH* were based on the study by Wang et al. [17] as follows: *LPCAT1* forward primer: 5'-ACC TAT TCC GAG CCA TTG ACC-3' and *LPCAT1* reverse primer: 5'-CCT AAT CCA GCT TCT TGC GAA C-3'. GAPDH forward primer: 5'-AAT CCC ATC ACC ATC TTC CAG-3' and GAPDH reverse primer: 5'-TCA CCC CAG CCT TCT CCA T-3'. The relative *LPCAT1* expression level was calculated using the $2^{-\Delta\Delta ct}$ method.

Statistical analysis

Statistical analyses were conducted using IBM SPSS software version 21 and GraphPad Prism version 9.5.0. Data normality was assessed employing the Kolmogorov-Smirnov test. The Mann–Whitney U test was used to compare the continuous variables exhibiting non-normal distribution. Pearson Chi-square or Fisher's Exact Test was applied to compare categorical variables. The prognostic impact of *LPCAT1* expression was analyzed by the log-rank test using the Kaplan-Meier curve and Cox regression analysis. A two-tailed *P*-value<0.05 was considered to be statistically

significant. The *P*-values were not adjusted in this study.

Results

Patients' characteristics

A total of 140 patients participated in this study, with 70 patients in each AML and ALL groups. Among the patients suffering from AML and ALL, 36 and 43 were male, respectively. Additionally, there were 70 healthy participants: 40 in the adult control group (19 males), and 30 in the pediatric control group (18 males). There was no statistically significant difference in age and gender between the AML and ALL groups and their healthy control counterparts ($P > 0.05$).

LPCAT1 expression levels in leukemic patients and healthy control groups

The median *LPCAT1* expression levels in AML and ALL patients were 11.1 (range: 0.5-22.6) and 10.7 (range: 0.5-19.2), respectively. These levels were significantly elevated in patients compared with healthy adult and pediatric control groups, where the respective medians were 1.5 (range: 0-8.4) and 0.8 (range: 0.1-6.3) ($P = 0.038$ and 0.032), as depicted in figure 1.

The correlation between LPCAT1 expression and patients' clinical characteristics

Based on the median levels of *LPCAT1* expression, patients were divided into $LPCAT1^{high}$ and $LPCAT1^{low}$ groups, with 35 patients in each group for both AML and ALL, as illustrated in tables 1 and 2. There was no statistically significant difference between $LPCAT1^{high}$ and $LPCAT1^{low}$ groups in terms of gender, age, white blood cell (WBC) count, platelet (PLT) count, hemoglobin (Hb), FAB and WHO classifications of AML and ALL patients ($P > 0.05$). While the WBC count was higher in the $LPCAT1^{high}$ group of ALL patients as compared with the $LPCAT1^{low}$ group, this difference was not statistically significant ($P > 0.05$).

The association between LPCAT1 expression and prognosis in AML and ALL patients

Among the 140 patients in this study, 129 patients with adequate follow-up data, including 64 AML and 65 ALL patients, were selected for survival analysis. The mean survival time in patients with high and low *LPCAT1* expression was 15.13 and 26.73 months in the AML group, and 31.64 and 46.98 months in the ALL cohort, respectively. The 5-year survival rate revealed that patients with elevated *LPCAT1* expression had shorter overall survival (OS) than those with lowered *LPCAT1* expression in both AML and ALL groups ($P = 0.013$ and 0.019, respectively) (Figure 2). Moreover, the multivariate Cox regression analysis of the impact of *LPCAT1* expression (high vs low) on OS showed that *LPCAT1* overexpression was an unfavorable prognostic factor, with significant associations in both AML ($P = 0.02$, Hazard ratio (HR) = 2.075, 95% confidence interval (CI) = 1.123-3.834) and ALL ($P = 0.04$, HR = 2.574, 95% CI = 1.123-3.834) (Tables 3 and 4).

The association between other clinical variables and prognosis in AML and ALL

As shown in tables 3 and 4, age was an adverse prognostic factor for OS in ALL patients ($P < 0.001$, HR = 1.189, and CI = 0.998-1.038). However, we found no association between other variables, such as gender, WBC, PLT, and Hb, and patients' prognosis in both AML and ALL groups ($P > 0.05$).

Discussion

The study results showed a statistically significant increase in *LPCAT1* expression in acute leukemia patients compared with healthy individuals. Moreover, our findings indicated that overexpression of *LPCAT1* is

associated with shorter survival in both AML and ALL patients.

Cytogenetic abnormalities, such as NPM1, CEBPA, and FLT3 mutations and aberrant expression of ERG and BAALC genes, have been identified as valuable prognostic indicators in AML. However, despite the significance of these well-established prognostic biomarkers, the accurate assessment of acute leukemia prognosis requires further research.[18, 19] The present study, therefore, was conducted to explore whether *LPACT1* expression could serve as a prognostic predictor in acute leukemia patients.

Lipid metabolism alterations activate the oncogenic signaling pathways in cancer cells.[20] *LPCAT1* is a cytosolic enzyme involved in the PC biosynthesis pathway,[21] and several studies reported their oncogenic roles in various cancers. In this regard, Gao et al. revealed that *LPCAT1* regulated cervical cancer progression through the JAK2/STAT3 signaling pathway.[22] Furthermore, Huang et al. demonstrated that *LPCAT1* knockdown significantly suppressed cell proliferation and induced cell cycle arrest at the G0/G1 phase in cutaneous squamous cell carcinoma.[23] Similarly, in clear cell renal cell carcinoma, *LPCAT1* knockdown led to the PC depletion and inhibition of cell proliferation, migration, and invasion.[9] A functional study conducted by Liu et al. showed that *LPCAT1* was a target of *miR-205*, and was essential for the proliferation of liver hepatocellular carcinoma, head and neck squamous cell carcinoma, and Lung adenocarcinoma.[24] Despite these findings, few studies have investigated the different roles of *LPCAT1*, especially its prognostic roles in hematological malignancies.[17]

Our results are in parallel with a previous study, conducted by Wang et al., also showed that *LPCAT1* expression is significantly linked to the survival of AML patients. Wang et al. proposed that *LPCAT1* expression could serve as a potential biomarker for prognosis and clinical management of AML patients.[17] In the present study, we found no significant difference between *LPCAT1*^{high} and *LPCAT1*^{low} patients concerning FAB and WHO classifications, neither in AML nor ALL patients. In contrast, Wang et al. reported that *LPCAT1* overexpression was associated with FAB-M4/M5 subclasses, Nucleophosmin (*NPM1*) mutation, and t (15;17) of AML patients.[17] This controversy between these two studies can be attributed to heterogeneity in patients' selection and study design. Additionally, in the present study, molecular tests, including NPM1, CEBPA, and FLT3 mutations, were not performed for all AML patients. Moreover, our study indicated that the overexpression of *LPCAT1* was related to a poor prognosis in both AML and ALL patients. However, Wang et al. study was only limited to AML patients. Our findings potentiate the prognostic significance of *LPCAT1* overexpression in AML presented by Wang et al. Most notably, our findings regarding *LPCAT1* overexpression and prognostic significance in ALL patients is the first report so far, and future investigations are warranted to further clarify the precise roles of *LPCAT1* in ALL patients.

Furthermore, several studies investigated the prognostic effects of *LPCAT1* in solid tumors. For instance, Zhang et al. and Li et al. demonstrated that up-regulation of *LPCAT1* was an independent predictor of prognosis in hepatocellular carcinoma.[25, 26] Similarly, a study conducted by Zhao T et al. showed the poor prognostic effects of *LPCAT1* overexpression in endometrial cancer.[27] In contrast, Bellon et al. found that *LPCAT1* was not related to the prognosis of patients with esophageal cancer.[28]

While our findings suggest that *LPCAT1* may serve as a promising prognostic indicator in acute myeloid and lymphoblastic leukemia,

there were limitations within our study. These include limited sample size, insufficient molecular data about key mutations like RUNX1, ASXL1, and TP53 that can influence patient prognosis, and focusing solely on the correlation between *LPCAT1* expression and OS without investigating the impact of patient responses to varied treatments. Furthermore, the results of the present study should be interpreted with caution, and more confirmatory prognosis studies in different ethnicities with larger sample sizes are warranted to validate our results.

Conclusion

According to the findings of this study, the expression levels of *LPCAT1* in patients with acute leukemia were significantly higher than in healthy controls, and the overexpression of *LPCAT1* was associated with shorter OS in these patients. *LPCAT1* was a potential prognostic biomarker in our patients with acute leukemia.

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Conflict of Interest

None declared.

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Table 1. Clinicopathological features of AML patients with high and low *LPCAT1* expression

Patient's parameters	**All patients**	**High *LPCAT1* expression (N=35)**	**Low *LPCAT1* expression (N=35)**	***P*-value**
Sex, male/female, N=70	36/34	17/18	19/16	0.632
Median age, years (range), N=70	38.5 (20-81)	40 (20-68)	37 (21-81)	0.511
Median WBC $(\times 10^9/L)$ (range), N=70	65.9 (2-285)	65.7 (2-285)	67.4 (3.8-253.4)	0.948
Median $Hb_{(g/dL)}$ (range), N=70	8.2 (4-14.3)	8.1 (5.9-13.6)	8.3 (4-14.3)	0.414
Median PLT $(\times 10^9/L)$ (range), N=70	55.5 (2-454)	56 (2-270)	55 (5.2-454)	0.589
FAB classification, N (%), N=70				0.239
M0	1 (1.4)	0 (0.0)	0 (2.9)	
M1	14 (20.0)	7 (20.0)	7 (20.0)	
M2	16 (22.9)	10 (28.6)	6 (17.1)	
M3	14 (20.0)	4 (11.4)	10 (28.6)	
M3v	2 (2.9)	0 (0.0)	2 (5.7)	
M4	10 (14.3)	5 (14.3)	5 (14.3)	
M4Eo	2 (2.9)	1 (2.9)	1 (2.9)	
M5	11 (15.7)	8 (22.9)	3 (8.6)	
WHO classification, N (%)				0.310
t (8;21), N=66	3 (4.3)	2 (5.7)	1 (2.9)	
t (15;17), N=63	14 (20.0)	4 (11.4)	10 (28.6)	
t (6;9), N=56	1 (1.4)	0 (0.0)	1 (2.9)	
inv (16), N=64	1 (1.4)	1 (2.9)	0 (0.0)	
Mutated *NPM1*, N=22	10 (14.3)	4 (11.4)	6 (17.1)	
Mutated *CEBPA*, N=17	1 (2.9)	1 (2.9)	1 (2.9)	
NOS	39 (55.7)	23 (65.7)	46 (45.7)	
Gene mutations				
FLT3-ITD (+/-), N=46	12/34	8/21	4/13	> 0.99
FLT3-TKD (+/-), N=46	4/42	1/28	3/14	0.135

AML: Acute myeloid leukemia; *LPCAT1*: *Lysophosphatidylcholine acyltransferases 1*; WBC: White blood cell; PLT: Platelet; Hb: Hemoglobin; FAB: French–American–British; WHO: World Health Organization; FLT3: Fms-related tyrosine kinase-3; ITD: Internal tandem duplication; NPM1: Nucleophosmin; CEBPA: CCAAT/Enhancer Binding Protein α; NOS: Not Otherwise Specified

Table 2. Clinicopathological features of ALL patients with high and low *LPCAT1* expression

Patient's parameters	**All patients**	**High *LPCAT1* expression (N=35)**	**Low *LPCAT1* expression (N=35)**	***P*-value**
Gender, male/female, N=70	43/27	23/12	20/15	0.461
Median age, years (range), N=70	5 (1-16)	5 (1-16)	5 (1-16)	0.146
Median WBC $(\times 10^9/L)$ (range), N=70	16.7 (3.1-270)	47.6 (5.5-256.8)	32.4 (3.1-270)	0.064
Median $Hb_{(g/dL)}$ (range), N=70	7.1 (3.7-18.4)	7.6 (4.6-11.1)	6.6 (3.7-18.4)	0.202
Median PLT $(\times 10^9/L)$ (range), N=70	73 (12-478)	75 (12-478)	58 (18-404)	0.421
FAB classification, N (%), N=70				0.811
L1	37 (52.9)	18 (51.4)	19 (54.3)	
L2	33 (47.1)	17 (48.6)	16 (45.7)	
WHO classification, N (%)				0.326
t (12;21), N=66	12 (17.1)	4 (11.4)	8 (22.9)	
t (1;19), N=66	2 (2.9)	2 (5.7)	0 (0.0)	
t (9;22), P190, N=70	3 (4.3)	1 (2.9)	2 (5.7)	
KMT2A (*MLL*) rearranged, N=66	0 (0.0)	0 (0.0)	0 (0.0)	
NOS	53 (75.7)	28 (80.0)	25 (71.4)	

ALL: Acute lymphoblastic leukemia; *LPCAT1*: *Lysophosphatidylcholine acyltransferases 1*; WBC: White blood cell; PLT: Platelet; Hb: Hemoglobin; FAB: French–American–British; WHO: World Health Organization; MLL: Mixed-Lineage or Myeloid-Lymphoid Leukemia; NOS: Not Otherwise Specified

Table 3. Multivariate analyses of variables for OS in AML patients

Variables	***P*-value**	**OS HR**	**CI**
Sex	0.71	1.116	0.619-2.012
Age (year)	0.07	1.018	0.998-1.038
LPCAT1 expression (High vs. Low)	0.02	2.075	1.123-3.834
WBC $(\times 10^9/L)$	0.25	1.003	0.998-1.008
$Hb_{(g/dL)}$	0.38	0.942	0.821-1.079
PLT $(\times 10^9/L)$	0.10	0.996	0.991-1.001

AML: Acute myeloid leukemia; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival; *LPCAT1*: *Lysophosphatidylcholine acyltransferases 1*; WBC: White blood cell; PLT: Platelet; Hb: Hemoglobin

Table 4. Multivariate analyses of variables for OS in ALL patients

Variables	***P*-value**	**OS HR**	**CI**
Sex	0.17	1.894	0.619-2.012
Age (year)	< 0.001	1.189	0.998-1.038
LPCAT1 expression (High vs. Low)	0.04	2.574	1.123-3.834
WBC $_{(\times 10^9/L)}$	0.10	0.993	0.998-1.008
Hb$_{(g/dL)}$	0.83	1.020	0.821-1.079
PLT $_{(\times 10^9/L)}$	0.49	0.998	0.991-1.001

ALL: Acute lymphoblastic leukemia; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival; *LPCAT1*: *Lysophosphatidylcholine acyltransferases 1*; WBC: White blood cell; PLT: Platelet; Hb: Hemoglobin

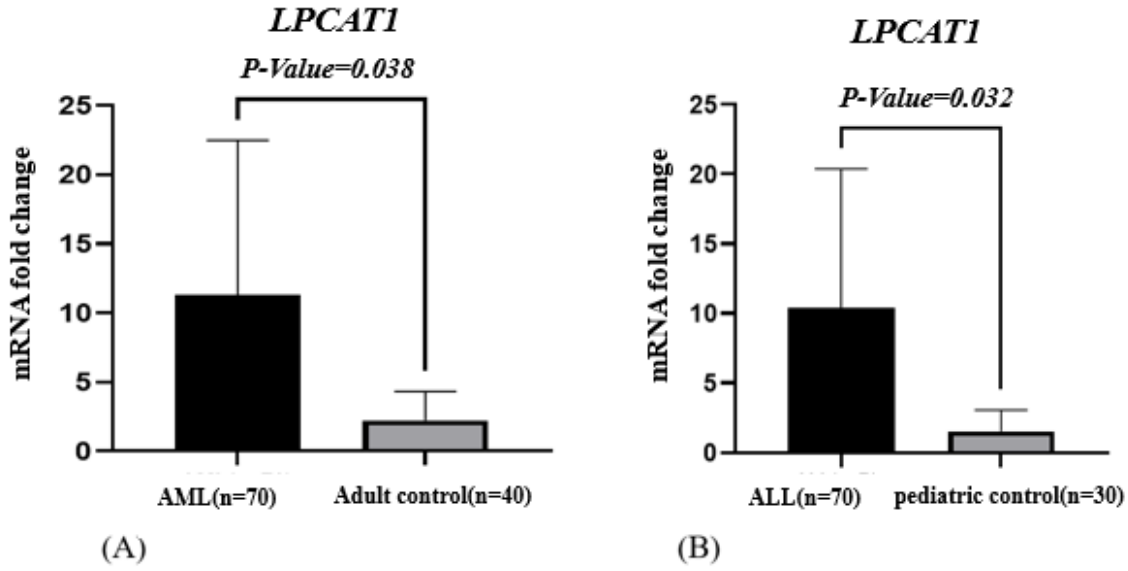

Figure 1. This figure shows the *LPCAT1* expression in patients and controls detected by RT-qPCR. (A) mRNA fold change level in AML patients compared with adult controls. (B) mRNA fold change level in ALL patients compared with pediatric controls.

AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; *LPCAT1: lysophosphatidylcholine acyltransferase 1*; RT-qPCR: Real-time quantitative polymerase chain reaction

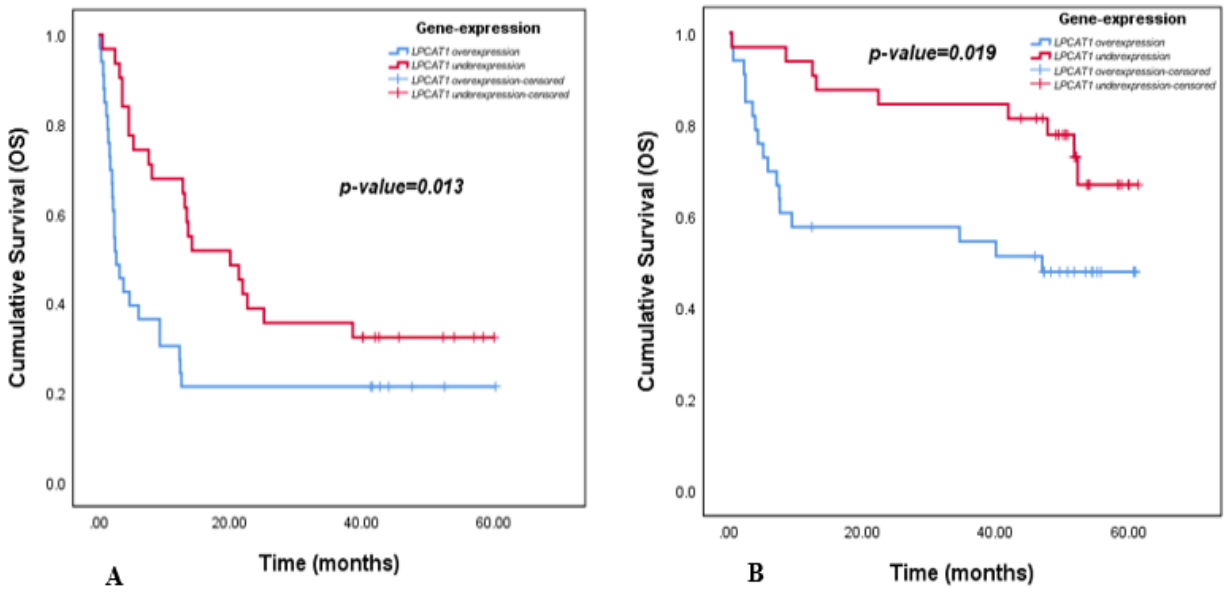

Figure 2. Kaplan-Meier analysis for OS, based on *LPCAT1* expression in AML (A) and ALL (B) patients. High expression of *LPCAT1* is associated with the shorter OS in both AML and ALL patients (P = 0.013 and 0.019, respectively).

AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; OS: Overall survival; *LPCAT1: lysophosphatidylcholine acyltransferase 1*