Identification of \textit{LPCAT1} expression as a potential prognostic biomarker guiding treatment choice in acute myeloid leukemia

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\textbf{Abstract.} Changes in lipid metabolism affect numerous cellular processes that are relevant to cancer biology, including cell proliferation, death, differentiation and motility. In the phosphatidylcholine biosynthesis pathway, the conversion of lysophosphatidylcholine (LPC) to phosphatidylcholine is catalyzed by cytosolic enzymes of the LPC acyltransferase (LPCAT) family. A number of studies have demonstrated that \textit{LPCAT1} overexpression is a frequent event in diverse human cancer types, and that it is associated with unfavorable pathological characteristics and patient survival. The aim of the present study was to explore the prognostic role of the expression of LPCAT family members in acute myeloid leukemia (AML). Using Cox regression analysis, only \textit{LPCAT1} expression was identified as an independent prognostic biomarker in AML. In a cohort from The Cancer Genome Atlas, Kaplan-Meier analysis revealed that patients with AML and higher expression levels of \textit{LPCAT1} had shorter overall survival (OS) and leukemia-free survival (LFS) times compared with those with lower expression levels of \textit{LPCAT1}. This was further confirmed using an independent cohort from The Gene Expression Omnibus. Using a third cohort comprising patients with AML and healthy volunteers, it was confirmed that \textit{LPCAT1} expression was significantly increased in newly diagnosed AML cases compared with healthy controls. Moreover, higher expression of \textit{LPCAT1} was associated with French-American-British subtype-M4/M5 and nucleophosmin 1 mutations. Notably, patients who underwent hematopoietic stem cell transplantation (HSCT) following induction therapy exhibited significantly longer OS and LFS times compared with patients who only received chemotherapy after induction therapy in the higher \textit{LPCAT1} expression group, whereas no significant differences in OS and LFS times were observed between the HSCT and chemotherapy groups among total cases of AML in the lower \textit{LPCAT1} expression group. These results suggest that patients with AML who exhibit higher \textit{LPCAT1} expression levels may benefit from HSCT. Collectively, the findings of the present study indicate that \textit{LPCAT1} expression may serve as an independent prognostic biomarker that can guide the choice between HSCT and chemotherapy in patients with AML.

\textbf{Introduction}

Acute myeloid leukemia (AML) is an aggressive hematological malignancy with an incidence rate of 3.7 per 100,000 worldwide, and it is characterized by the clonal proliferation of myeloid hematopoietic stem cells with the inhibition of normal hematopoiesis (1). AML is a highly heterogeneous disease in terms of clinical presentation, cytogenetics/genetics and clinical outcome (1). Due to its considerable variability, it is recommended that AML treatment should be more personalized and precisely targeted based on the risk classifications of each patient (2). At present, the European LeukemiaNet risk classification is widely used in the clinical management of AML; however, there is marked heterogeneity among patients in clinical practice, particularly those in intermediate groups in the classification system (2). Therefore, it is crucial to identify novel potential prognostic and predictive biomarkers to improve our understanding of leukemogenesis so that molecular-based stratification can be applied to risk-adapted therapies and ultimately improve the clinical outcome of AML.

Changes in lipid metabolism affect numerous cellular processes that are relevant to cancer biology, including cell proliferation, death, differentiation and motility (3). In the phosphatidylcholine biosynthesis pathway, the conversion of lysophosphatidylcholine (LPC) to phosphatidylcholine is catalyzed by cytosolic enzymes of the LPC acyltransferase (LPCAT) family (4). To date, \textit{LPCAT1}, \textit{LPCAT2}, \textit{LPCAT3} and \textit{LPCAT4} have been identified and partially characterized as the four members of the LPCAT family. A number of studies have demonstrated that the overexpression of \textit{LPCAT1} is frequent in diverse human cancer types, including prostate cancer (5,6), breast cancer (7,8), gastric cancer (9), clear cell renal cell carcinoma (10), lung cancer (11), hepatocellular carcinoma (12), oral squamous cell carcinoma (13) and colorectal cancer (14). Moreover, \textit{LPCAT1} overexpression has been found to be associated with unfavorable pathological characteristics and survival in several types of cancer (5-11).

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However, the potential roles and clinical implications of LPCAT family members in AML remain poorly investigated. Therefore, the aim of the present study was to investigate the prognostic role of the expression of LPCAT family members in AML, and to determine whether this has the potential to be used as a new biomarker for the diagnosis and prognosis of AML, and for the optimization of clinical decision-making in the treatment of the disease.

Materials and methods

Patients. The first cohort included in the present study comprised 173 patients with AML for whom LPCAT family (LPCAT1/2/3/4) expression data were available from The Cancer Genome Atlas (TCGA) database (TCGA-LAML, NEJM 2013) (https://cancergenome.nih.gov/ and http://www.cbioportal.org/) (15). The clinical and molecular characteristics obtained for the cohort included age (median, 58 years; age range, 18-88 years), sex (81 male and 92 female), white blood cell (WBC) counts, peripheral blood (PB) blasts, bone marrow (BM) blasts, French-American-British (FAB) subtype, karyotype and the frequencies of known common genetic mutations, as well as gene expression levels. Due to the independent disease entity of patients with FAB-M3, the non-M3 AML cohort was used in the survival analysis. Following induction chemotherapy, 100 of the patients received only chemotherapy as a consolidation treatment, whereas 73 patients underwent hematopoietic stem cell transplantation (HSCT) with/without chemotherapy as a consolidation treatment. This cohort of patients with AML was used for the identification of LPCAT family members whose expression was associated with prognosis, and for the analysis of the clinical implications of LPCAT1 expression.

A second cohort was also included, comprising 78 patients (median age, 62 years, age range 18-85 years) with cytogenetically normal AML (CN-AML) from a Gene Expression Omnibus (GEO) dataset (GSE12417) (16). The online tool GenomicScape (http://genomicscape.com/microarray/survival.php) was applied to validate the prognostic value of LPCAT1 expression among the patients with CN-AML in this cohort (17).

A third cohort, comprising 48 patients with AML (26 male and 22 female; median age, 60 years; age range, 18-82 years) and 20 healthy volunteers (11 male and 9 female; median age, 56 years; age range, 18-71 years) from Jiangyin People's Hospital (Jiangyin, China), was also enrolled in the present study. All the patients with AML were treated at Jiangyin People's Hospital between June 2015 and December 2018. This cohort of patients with AML was used for the identification of LPCAT1 expression in patients with AML.

Sample preparation, RNA isolation and reverse transcription. PB samples were examined to identify the changes in LPCAT1 expression that occur during the development of AML since PB contains blasts, and the collection of BM samples from patients with AML in the medical laboratory of Jiangyin People's Hospital (Jiangyin, China) was challenging. PB samples were collected from the 20 controls and the 48 patients with AML at diagnosis, and from 15 of the patients with AML at complete remission (CR). Neculated cells were obtained from PB using red blood cell lysis buffer (Beijing Solarbio Science & Technology Co., Ltd.). Total RNA was extracted from the PB nucleated cells using TRizol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.). Reverse transcription was performed to synthesize cDNA from the RNA using the PrimerScript™ RT reagent kit (Takara Bio, Inc.) according to the manufacturer's instructions.

Quantitative PCR (qPCR) analysis. qPCR analysis was conducted to detect LPCAT1 and GAPDH transcripts using TB Green Premix Ex Taq™ II (Takara Bio, Inc.). The primers used were as follows: LPCAT1 forward, 5'-ACCTATTTCCGAGCATGTGACC-3' and reverse, 5'-CTCTAATCCAGCTTCTTGGCAG-3'; and GAPDH forward, 5'-AATCCCCATACACCCTTCCAGC-3' and reverse, 5'-GAGCCCCAGCTTCTCCAT-3'. GAPDH served as the reference gene. qPCR conditions were as follows: 95°C for 30 sec, followed by 40 cycles of 95°C for 10 sec, 60°C for 1 min, 72°C for 1 min, and 80°C for 30 sec. The relative LPCAT1 transcript level was calculated using the 2^(- ΔΔCt) method (20).

Statistical analysis. The Mann-Whitney U test or the Kruskal-Wallis test followed by Dunn's post hoc test was used for the comparison of continuous variables, and Pearson's χ² or Fisher's exact test were used for the comparison of categorical variables. The effect of LPCAT1 expression on leukemia-free survival (LFS) and overall survival (OS) was analyzed using the Kaplan-Meier method with log-rank test, and Cox regression analysis. Two-tailed P-values of <0.05 in all statistical analyses were considered to indicate a statistically significant difference.

Results

Identification of prognosis-associated LPCAT family member expression in AML. To investigate the prognostic value of LPCAT family members in AML, expression data on all LPCAT family members (LPCAT1/2/3/4) in AML were extracted from TCGA. The prognostic value of LPCAT1/2/3/4 expression was investigated following the division of the patients into two groups (lower and higher) by the median level of LPCAT1/2/3/4 mRNA (1161.1579:2249.6413:1218.6589:477.0187). The results of Cox regression univariate analysis revealed that LPCAT1/2/3 expression was associated with OS in AML, and LPCAT3 expression was associated with LFS, whereas LPCAT1/2 expression showed a trend being associated with LFS (Table I). However, despite the well-known prognostic factors (age, WBC and ELN risks) showing significant associations, only LPCAT1 expression was identified as an independent prognostic biomarker in AML by Cox regression multivariate analysis, and exhibited a significant association with OS (Table I). Furthermore, Kaplan-Meier analysis also demonstrated that patients with higher expression levels of LPCAT1 exhibited significantly shorter OS time compared with those with lower expression of LPCAT1 among the patients with AML.
Validation of LPCAT1 expression with prognosis in AML. To validate the prognostic value of LPCAT1 expression in AML, GEO data (GSE12417) on 78 patients with CN-AML were analyzed using the online web tool GenomicScape. Kaplan-Meier analysis revealed that the patients with higher expression levels of LPCAT1 presented significantly shorter OS times compared with those with lower expression levels of LPCAT1 (Fig. 1C).

Validation of LPCAT1 overexpression in newly diagnosed cases of AML. In order to further explore the expression of LPCAT1 in AML, the mRNA levels of LPCAT1 in patients newly diagnosed with AML were further examined. According to the RT-qPCR results for the third cohort, LPCAT1 expression was significantly increased in patients with newly diagnosed AML compared with that in normal controls (Fig. 2). Furthermore, LPCAT1 expression levels in patients with AML at CR were significantly lower compared with those in patients with newly diagnosed AML (Fig. 2).

Clinical implications of LPCAT1 expression in AML. Due the significant prognostic value of LPCAT1 expression in AML, the associations of LPCAT1 expression with the clinical and biological characteristics of patients were further investigated, based on TCGA data. As shown in Table II, no significant differences were identified between patients with lower and higher levels of LPCAT1 expression in terms of sex, age, WBC count and BM blasts (P>0.05). However, patients with higher expression of LPCAT1 exhibited lower numbers of PB blasts compared with patients with lower expression of LPCAT1 (P=0.001). Moreover, significant differences were detected between the two groups regarding the distribution of FAB classification subtypes and cytogenetic features (P<0.001 and P=0.033, respectively). Patients with higher expression of LPCAT1 were frequently classified as FAB-M4/M5 (P=0.002 and P<0.001, respectively) and less frequently as FAB-M3 or t(15;17) (P=0.063 and P=0.028, respectively). In addition, associations of LPCAT1 expression with common gene expression and mutations in AML were also observed (Table II). Higher LPCAT1 expression was associated with nucleophosmin 1 (NPM1) mutation, isocitrate dehydrogenase 1 (IDH1) wild-type and CCAAT/enhancer-binding protein α (CEBPA) wild-type (P=0.018, P=0.063 and P=0.080, respectively).
Moreover, LPCAT1 expression was further compared between patients with and without NPM1, IDH1, CEBPA, and TP53 gene mutations, and the differences between the wild-type and mutant groups were observed to be statistically significant for all four genes (Fig. 3).

Patients with AML and higher LPCAT1 expression may benefit from HSCT. To investigate whether HSCT is able to overcome the adverse outcomes associated with higher expression of LPCAT1, the survival times of patients who had or had not received HSCT after induction chemotherapy were compared in the lower and higher LPCAT1 expression groups. In the higher LPCAT1 expression group, the patients who had undergone HSCT following induction therapy exhibited significantly longer OS and LFS times compared with those who only received chemotherapy. In the lower LPCAT1 expression group, no significant differences were observed in OS and LFS between patients who had undergone HSCT and those who had not among total-AML and only in LFS among non-M3-AML cases. These results suggest that patients with AML and higher LPCAT1 expression may benefit from HSCT, and LPCAT1 expression may guide the decision of whether to select HSCT or chemotherapy as an appropriate treatment for patients with AML after induction therapy.

Discussion

Studies have demonstrated the biological role of LPCAT1 in diverse human cancer types. For example, Morita et al (12) reported that the overexpression of LPCAT1 promoted the proliferation, migration, and invasion of hepatocellular carcinoma cells. In addition, in oral squamous cell carcinoma cell lines, the knockdown of LPCAT1 resulted in decreased cellular proliferation, invasiveness, and migration, as well as decreased intercellular platelet-activating factor (PAF) concentration and PAF receptor expression (13). Furthermore, Du et al (10) revealed that LPCAT1-knockdown in clear cell renal cell carcinoma inhibited cell proliferation, migration, and invasion, and induced cell cycle arrest at the G0/G1 phase.
Table II. Association of LPCAT1 expression with clinicopathological characteristics in patients with acute myeloid leukemia.

| Parameters                      | Low (n=87) | High (n=86) | P-value |
|---------------------------------|------------|-------------|---------|
| LPCAT1 expression               |            |             |         |
| Sex, male/female                | 42/45      | 39/47       | 0.761   |
| Age, median (range), years      | 57 (18-82) | 58.5 (22-88)| 0.311   |
| Median WBC count (range), x10^9/l | 18.7 (0.5-297.4) | 15.6 (0.4-137.2) | 0.808   |
| Median PB blasts (range), %     | 50 (0-98)  | 18 (0-94)   | 0.001   |
| Median BM blasts (range), %     | 72 (30-99) | 73 (30-100) | 0.449   |
| FAB classification, n           |            |             | <0.001  |
| M0                              | 12         | 4           | 0.063   |
| M1                              | 26         | 18          | 0.222   |
| M2                              | 23         | 15          | 0.199   |
| M3                              | 12         | 4           | 0.063   |
| M4                              | 9          | 25          | 0.002   |
| M5                              | 2          | 16          | <0.001  |
| M6                              | 1          | 1           | 1.000   |
| M7                              | 1          | 2           | 0.621   |
| No data                         | 1          | 1           | 1.000   |
| Cytogenetics, n                 |            |             | 0.033   |
| Normal                          | 39         | 41          | 0.761   |
| t(15;17)                        | 12         | 3           | 0.028   |
| t(8;21)                         | 2          | 5           | 0.278   |
| inv(16)                         | 5          | 5           | 1.000   |
| +8                              | 6          | 2           | 0.278   |
| del(5)                          | 0          | 1           | 0.497   |
| -7/del(7)                       | 6          | 1           | 0.117   |
| 11q23                           | 0          | 3           | 0.121   |
| Others                          | 5          | 9           | 0.280   |
| Complex                         | 10         | 15          | 0.288   |
| No data                         | 2          | 1           | 1.000   |
| Gene mutation, n                |            |             |         |
| FLT3 (+/-)                      | 20/67      | 29/57       | 0.131   |
| NPM1 (+/-)                      | 17/70      | 31/55       | 0.018   |
| DNMT3A (+/-)                    | 18/69      | 24/62       | 0.292   |
| IDH2 (+/-)                      | 12/75      | 5/81        | 0.124   |
| IDH1 (+/-)                      | 12/75      | 4/82        | 0.063   |
| TET2 (+/-)                      | 10/77      | 5/81        | 0.280   |
| RUNX1 (+/-)                     | 9/78       | 6/80        | 0.590   |
| TP53 (+/-)                      | 4/83       | 10/76       | 0.103   |
| NRAS (+/-)                      | 3/84       | 8/78        | 0.132   |
| CEBPA (+/-)                     | 10/77      | 3/83        | 0.080   |
| WT1 (+/-)                       | 7/80       | 3/83        | 0.329   |
| PTPN11 (+/-)                    | 3/84       | 5/81        | 0.496   |
| KIT (+/-)                       | 3/84       | 4/82        | 0.720   |
| U2AF1 (+/-)                     | 4/83       | 3/83        | 1.000   |
| KRAS (+/-)                      | 3/84       | 4/82        | 0.720   |
| SMC1A (+/-)                     | 3/84       | 4/82        | 0.720   |
| SMC3 (+/-)                      | 2/85       | 5/81        | 0.278   |

Patient data are derived from TCGA database (TCGA-LAML, NEJM 2013) (15). FLT3 mutations include FLT3-internal tandem duplication (ITD) and FLT3-tyrosine kinase domain (TKD). CEBPA mutations include double and single allele mutations. LPCAT1, lysophosphatidylcholine acyltransferase 1; WBC, white blood cell; PB, peripheral blood; BM, bone marrow; FAB, French-American-British; TCGA, The Cancer Genome Atlas; FLT3, FMS-like tyrosine kinase 3.
Figure 3. Associations of LPCAT1 expression with gene mutations in AML. Data on patients with AML are derived from TCGA database (TCGA-LAML, NEJM 2013) (15). LPCAT1 expression in AML patients with and without NPM1, IDH1, CEBPA and TP53 mutations. LPCAT1, lysophosphatidylcholine acyltransferase 1; AML, acute myeloid leukemia; NPM1, nucleophosmin 1; IDH1, isocitrate dehydrogenase 1; CEBPA, CCAAT/enhancer-binding protein α; TCGA, The Cancer Genome Atlas; WT, wild-type; mu, mutant.

Figure 4. Effect of HSCT on the survival of patients with AML in groups with different LPCAT1 expression levels. Data on patients with AML are derived from TCGA database (TCGA-LAML, NEJM 2013) (15). Kaplan-Meier survival curves of (A) OS and (B) LFS among whole-cohort AML in patients with higher LPCAT1 expression. Kaplan-Meier survival curves of (C) OS and (D) LFS among patients with non-M3 AML and higher LPCAT1 expression. Kaplan-Meier survival curves of (E) OS and (F) LFS among whole-cohort AML in patients with lower LPCAT1 expression. Kaplan-Meier survival curves of (G) OS and (H) LFS among patients with non-M3 AML and lower LPCAT1 expression. HSCT, hematopoietic stem cell transplantation; AML, acute myeloid leukemia; LPCAT1, lysophosphatidylcholine acyltransferase 1; OS, overall survival; LFS, leukemia-free survival.
Moreover, short hairpin RNA-mediated LPCAT1 silencing in lung adenocarcinoma not only abrogated cell proliferation, migration and invasion in vitro, but also arrested tumor growth and brain metastases in vivo (11). Mechanically, LPCAT1 dysregulation has been shown to at least partially affect the progression of lung adenocarcinoma through the PI3K/AKT signaling pathway via the targeting of MYC transcription (11). However, studies investigating the direct role of LPCAT1 in AML are lacking. Therefore, further functional and clinical studies are required to investigate the potential role of LPCAT1 during leukemogenesis in AML.

The present study investigated the clinical implications of the expression of LPCAT family members in AML, and demonstrated that LPCAT1 expression is significantly associated with the survival of patients with AML. In addition, the present study indicated that LPCAT1 expression may act as a potential biomarker to guide the choice between HSCT and chemotherapy for the further treatment of patients with AML after induction therapy. These results emphasize the potential of LPCAT1 expression as a valuable indicator for the clinical management of AML. Although this is, to the best of our knowledge, the first study to report the clinical significance of LPCAT1 expression in AML, a number of studies have demonstrated the prognostic role of LPCAT1 expression in numerous solid tumors. For example, Zhou et al (5) reported that LPCAT1 expression was associated with the progression of prostate cancer independently of patient ethnicity and age, prostate-specific antigen level and the positivity of surgical resection margins, and suggested that it may be a novel biomarker for the diagnosis and prognosis of prostate cancer, as well as for studying its pathogenesis. Furthermore, Grupp et al (6) demonstrated that high LPCAT1 expression independently predicted a high risk of biochemical recurrence in prostate cancer. In breast cancer, LPCAT1 expression has been shown to be significantly associated with tumor grade and TNM stage, as well as increased proliferative activity, negative estrogen receptor status, negative progesterone receptor status, positive human epithelial growth factor receptor 2 status, and deletions of phosphatase and tensin homolog and cyclin-dependent kinase inhibitor 2A (7,8), with multivariate analysis revealing that upregulated LPCAT1 expression is an independent predictor of early tumor recurrence in breast cancer (8). Uehara et al (9) reported that LPCAT1 expression was positively associated with tumor differentiation and negatively associated with the depth of tumor invasion, lymph node metastasis and tumor stage in gastric cancer. In addition, Du et al (10) revealed that LPCAT1 expression was significantly associated with higher tumor grade, higher TNM stage, larger tumor size and shorter OS time in clear cell renal cell carcinoma. Moreover, LPCAT1 expression was found to negatively impact prognosis in lung adenocarcinoma (11). Thus, it may be inferred that LPCAT1 expression plays a key role in AML and the treatment response following HSCT. However, the associations between LPCAT1 expression and AML biology require further investigation.

The NPM1 gene encodes a multifunctional protein that shuttles between the nucleus and cytoplasm, and has prominent nucleolar localization. NPM1 mutations are common in AML and comprise a unique subtype in the 2016 WHO classification of hematopoietic neoplasms (19). NPM1 mutations represent the most common genetic lesion in adult AML and cause the aberrant cytoplasmic delocalization of NPM1 mutants. NPM1 mutants have been demonstrated to maintain the leukemic state through homeobox gene overexpression (21). The present study identified a link between LPCAT1 and NPM1 mutations in patients with AML. However, the exact association between LPCAT1 expression and NPM1 mutations remains poorly defined. Further studies are required to determine the potential mechanism by which the overexpression of LPCAT1 contributes to the leukemogenesis caused by NPM1 mutations.

In conclusion, the findings of the present study indicate that LPCAT1 expression may serve as an independent prognostic biomarker to guide the treatment choice between HSCT and chemotherapy in patients with AML.

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Availability of data and materials

TCGA database (TCGA-LAML, NEJM 2013; https://cancer.genome.nih.gov/ and http://www.cbioportal.org/) and GEO (GSE12417) data are available online. The other datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

JL conceived and designed the study. KW, ZW and YS analyzed the data. WT, XX and YC performed the experiments; KW and JL wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in the study were approved by the Ethics Committee of Jiangyin People’s Hospital and complied with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients included in this study.

Patient consent for publication

Not applicable.

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