



Altered expression of genes involved in the serine synthesis pathway (SSP) in patients with acute myeloid leukemia

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Abstract

Background: Acute myeloid leukemia (AML) is characterized by the uncontrolled proliferation of malignant cells, which rely on various metabolic pathways to sustain their survival and growth. In this regard, the serine synthesis pathway (SSP) is critically involved in generating biological macromolecules and oncogenic metabolites that are fundamental in tumor growth and proliferation. As a result, this study aimed to assess the expression of SSP-related genes, including Phosphoserine aminotransferase (PSAT1), phosphoglycerate dehydrogenase (PHGDH), and 1-3-phosphoserine phosphatase (PSPH) in AML patients.

Methods: Quantitative real-time polymerase chain reaction (qRT-PCR) was used to assess the expression of PHGDH, PSAT1, and PSPH genes in samples from 60 newly diagnosed AML patients and 10 healthy controls.

Results: Our investigation revealed decreased expression of PSAT1 and PSPH in AML patients compared to controls ($P=0.002$, $P=0.026$, respectively). However, no significant change was observed in PHGDH expression. Moreover, positive correlations were identified between the expression levels of PHGDH and PSAT1 ($r=0.488$, $P=0.0002$), PHGDH and PSPH ($r=0.379$, $P=0.007$), and PSAT1 and PSPH ($r=0.331$, $P=0.01$) in AML patients.

Conclusion: Although malignant cells are exposed to serine restriction, it seems that SSP up-regulation is not beneficial to myeloid blasts. This may be justified by applying alternative sources to compensate required serine for these cells. More investigations can shed light on the importance of alternative sources as therapeutic targets in AML patients.

Keywords: Serine biosynthesis, Phosphoglycerate dehydrogenase, Phosphoserine aminotransferase, Phosphoserine phosphatase

Citation: Khadem P, Keshavarz A, Mohammadi MH, Mezginejad F, Allahbakhshian Farsani M. Altered expression of genes involved in the serine synthesis pathway (ssp) in patients with acute myeloid leukemia. *Journal of Kerman University of Medical Sciences*. 2025;32:3660. doi:10.34172/jkmu.3660

Received: April 26, 2023, Accepted: April 29, 2025, ePublished: May 11, 2025

Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy characterized by the abnormal proliferation and differentiation of hematopoietic stem cells, leading to the accumulation of immature myeloid cells (1-3). The tumorigenesis process of AML is very complex, and evidence suggests that aberrant DNA methylation patterns initiate AML pathogenesis (4). The methylation process is involved in a wide range of vital intracellular activities and is fundamental for highly proliferative cells, especially for tumor growth and progression. Also, methylation of histones and DNA is the main process that contributes to epigenetic changes. Metabolic mediators afford epigenetic regulation; as a result, the aberrant metabolic function can lead to malignancy (5). S-adenosylmethionine (SAM) serves as the primary methyl donor in intracellular

methylation processes. Serine metabolism influences these methylation responses by contributing to SAM production via one-carbon metabolism pathways (6).

Serine is a non-essential amino acid that could strongly support numerous metabolic pathways, including the synthesis of nucleotides and antioxidants as well as the methyl producers required for methylation (7). Emerging evidence suggests considerable dependency of many cancer cells on this amino acid, including a study by Polet et al that reported serine plays a vital role in the growth and survival of leukemia cells, especially when the utilization of glutamine in metabolic processes is blocked (8). On the other hand, serine can be acquired through cellular uptake or endogenously synthesized from glycolytic intermediates through the serine synthesis pathway (SSP). Carbons derived from glucose



are redirected into the SSP via 3-phosphoglycerate as a glycolysis intermediate. Phosphoserine aminotransferase (PSAT), phosphoglycerate dehydrogenase (PHGDH), and 1-3-phosphoserine phosphatase (PSPH) are metabolic enzymes that catalyze the synthesis of serine and have been shown to have a role in tumorigenesis (9).

Previous studies have demonstrated that normal hematopoietic and leukemic cell growth will be inhibited in the absence of serine (10). In addition, since the SSP is intricately linked to the production of methyl donors necessary for methylation, and considering the pivotal role of epigenetic mechanisms in the development and progression of AML, this study was conducted to investigate the expression patterns of SSP-related genes, including PHGDH, PSAT1, and PSPH in leukemic blasts of AML patients in comparison with the control group. The result of this study may reveal a novel pathway involved in the pathogenesis of the disease, offering valuable insights for the development of targeted therapeutic strategies.

Methods

Study population

Bone marrow (BM) aspiration of 38 suspected AML patients and peripheral blood (PB) samples of 22 newly diagnosed AML cases referred to the Taleghani Hospital (Tehran, Iran) were collected in EDTA tubes. AML diagnosis of samples was confirmed by Morphology features, immunophenotyping, and molecular characteristics. Also, 10 BM and PB specimens (6 BM and 4 PB) from patients with no hematologic malignancies were collected as control samples. As bone marrow aspiration in normal individuals was impossible in our center, BM samples were collected from individuals in the remission phase of hematology malignancy. They were undergoing no medical treatment, and their BM pattern was normal at the time of sampling. Written consent was obtained from all participants, including patient and control individuals. Characteristics of AML patients are summarized in Table 1.

Table 1. Patient characteristics

Patient characteristics	
Age (y), Median (range)	36 (3-74)
Gender, No. (%)	
Male	35 (58.3%)
Female	25 (41.7%)
Sample type, No. (%)	
Peripheral blood	22 (36.7%)
Bone marrow	38 (63.3%)
Classification (FAB) (%)	(%)
M3	32%
Non M3	68%
Blast percentage (%), Median (range)	70 (35–96)

RNA extraction and cDNA synthesis

Total cellular RNA extraction was performed using RNeasy Kit (Qiagen, Germany). Then, to assess RNA samples' purity, the RNA OD was measured on NanoDrop (Thermo Scientific, USA), and expected OD ratios of 260/280 nm > 1.8 for all RNA samples were displayed. Subsequently, 1 µg of each RNA sample was utilized for cDNA synthesis reaction by means of a cDNA Synthesis Kit (Thermo Scientific, USA).

Primer design and real-time PCR

Primers were designed via Gene Runner and AlleleID software, and the specificity of these primers was checked in the Primer Blast NCBI database (Table 2). ABL gene was selected as a housekeeping gene to normalize the Ct value obtained from PCR reactions in this study. Subsequently, PHGDH, PSAT, PSPH, and ABL gene expressions in patient and control specimens were evaluated using real-time PCR (Rotor-Gene 6000, Qiagen, Germany). The PCR reaction mixture preparation was comprised of 7.5 µL of Real Plus 2x Master Mix Green- Low ROX (Ampliqon, Denmark), 1 µL of forward and reverse primers, 2 µL of template target cDNA and 4.5 µL of water to achieve a total volume of 15 µL. A standard curve for each target gene was drawn to obtain the efficiency of each PCR reaction, using four serial dilutions (1, 0.1, 0.01, and 0.001) of an appropriate cDNA sample. The thermal cycler program was defined for each reaction as follows: hold temperature 95 °C for 10 minutes, denaturation at 95°C for 15 seconds, and annealing at 55 °C and 61 °C (for PHGDH and PSAT1, respectively) for 15 seconds, and extension at 72 °C for 15 seconds. The thermal cycler profile for PSPH was denaturation at 95 °C for 30 seconds, annealing at 61 °C for 9 seconds, and extension at 72 °C for 9 seconds. Assessments were performed in duplicate, and the Livak method ($2^{-\Delta\Delta CT}$) was employed to calculate the fold change of each target gene.

Statistical analysis

The SPSS statistical software version 16.0 and Graph Pad Prism version 6.07 were applied to analyze and plot graphs of the obtained data. To assess the normal distribution of data, the Shapiro-Wilk test was selected. T-test for two-

Table 2. Primers sequences

Gene	Direction	Primer sequence
PHGDH	Forward	GCCCTTACCACTGCCTTCTCTC
	Reverse	GCGTTCACCAAGTTCACATCCG
PSAT	Forward	AACCTCCTGTCCAAGCCAG
	Reverse	TTGTATTCCAGGACCGAG
PSPH	Forward	CAGGTGCAGAGACTCATAG
	Reverse	AAAGCCACCAGATATTAGG
ABL	Forward	TGGAGATAACACTCTAAGCATAACTAAAGGT
	Reverse	GATGTAGTTGCTTGGGACCCA

state variables was used according to the Shapiro-Wilk test. Finally, the Pearson test was performed to investigate the correlation between gene expression. Statistical significance was considered at $P < 0.05$.

Results

PHGDH, PSAT, and PSPH gene expression levels in AML patients and control samples

PHGDH expression evaluation showed no significant alteration in AML patients compared to normal control samples ($P=0.290$). Our results revealed a statistically significant decrease in the expression of PSAT ($P=0.002$) and PSPH ($P=0.026$) in AML patients in comparison with control samples (Figure 1).

PHGDH, PSAT, and PSPH gene expression levels in M3 AML patients in comparison with Non-M3 AML cases

Our statistical analysis demonstrated no significant

differences in SSP genes expression in patients with M3 and Non-M3 acute myeloid leukemia (Figure 2).

Comparison between male and female gene expression levels of PHGDH, PSAT, and PSPH in AML patients

The differences in gene expression levels of PSAT1 ($P=0.004$) and PSPH ($P=0.049$) were significant in males compared to females, while there was no significant change in PHGDH gene expression between genders (Figure 3).

PHGDH, PSAT, and PSPH gene expression levels in < 50 and > 50 years old AML patients

The expression levels of the PHGDH, PSAT1, and PSPH genes in AML patients were compared between two age groups: those over 50 years (> 50) and those under 50 (< 50). No significant differences were seen in SSP gene expression in AML cases in these two age categories (Figure 4).

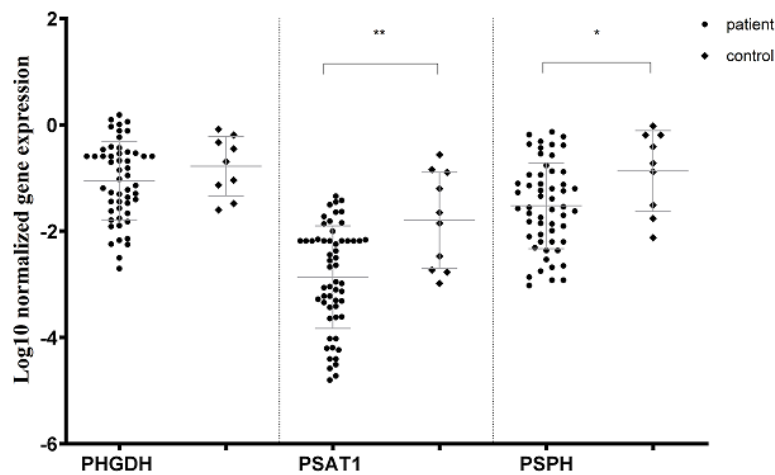


Figure 1. The mRNA expression levels of PHGDH, PSAT1, and PSPH in AML patients were compared with control samples by reporting Mean $\pm$ SEM. No significant difference ($P=0.290$) was observed between PHGDH expression levels in AML patients 0.26 ± 0.056 compared to control samples 0.30 ± 0.092 . A significant difference was observed between PSAT1 expression level in AML patients 0.01 ± 0.002 compared to control samples 0.07 ± 0.028 ($P=0.002$). A significant difference between PSPH expression levels in AML patients was observed in 0.12 ± 0.026 compared to control samples of 0.33 ± 0.108 , confirmed by a significant level ($P=0.026$). (** $P < 0.01$, * $P < 0.05$)

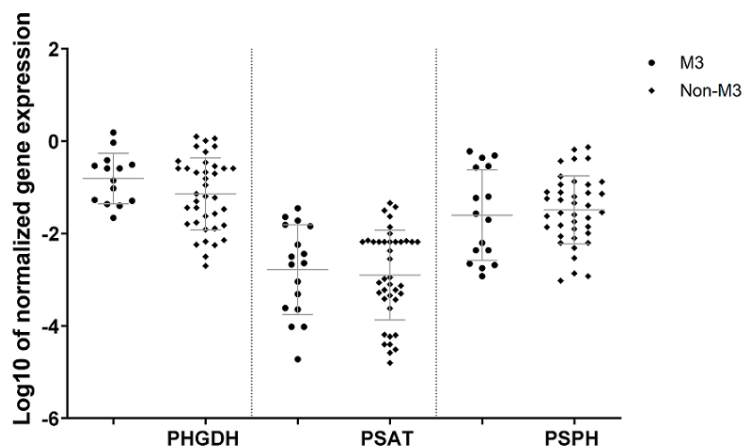


Figure 2. The scatter dot plot of PHGDH, PSAT1, and PSPH gene expression in M3 and non-M3 subgroups of AML patients represented as mean $\pm$ SD. Log 10 was calculated to obtain a normal distribution of data. There was no significant difference ($P > 0.05$) in gene expression level of these genes in M3 and non-M3 AML patients

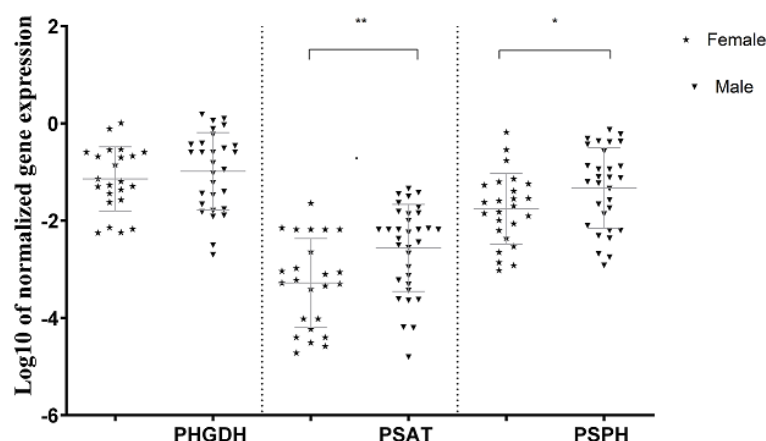


Figure 3. The scatter dot plot illustrates the gene expression levels of PHGDH, PSAT1, and PSPH in males compared to females, represented as Mean $\pm$ SD. Log10 was applied to achieve a normal distribution of the data. PSAT1 ($P=0.004$) and PSPH ($P=0.049$) showed significant differences in gene expression between males and females. However, there was no significant change in the gene expression of PHGDH between genders (** $P<0.01$, * $P<0.05$)

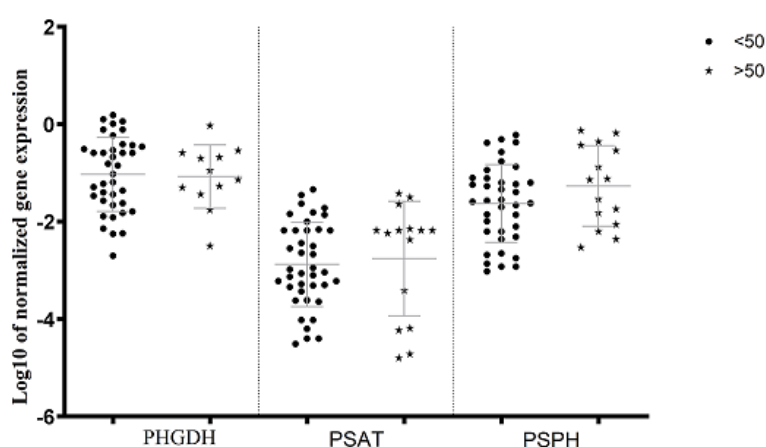


Figure 4. Scatter dot plot of the PHGDH, PSAT1, and PSPH gene expression levels in AML patients in two age groups of >50 and <50 , represented as Mean $\pm$ SD. No significant differences were observed between these two age categories ($P>0.05$)

Correlation between expression levels of PHGDH, PSAT, and PSPH genes

Statistical correlation analysis indicated a significant positive correlation between gene expression levels of PHGDH and PSAT ($r=0.488$ $P=0.0002$), PHGDH and PSPH ($r=0.379$ $P=0.007$), and PSAT and PSPH ($r=0.331$, $P=0.01$) in AML patients (Figure 5).

Discussion

Proliferating cells use various metabolic pathways to provide adequate amounts of necessary elements for their growth and survival. In this regard, the SSP, as one of the most important branches of glycolysis, has a crucial role in de novo serine generation (11,12). Moreover, the amino acid serine has a crucial role in producing methyl groups for methylation reactions (7). The methylation process is involved in a wide range of vital intracellular activities and is fundamental for highly proliferative cells, especially for tumor growth and progression (13). Methylation reactions seem to be highly involved in unique features of malignant myeloid blasts, such as global hypermethylation and limitless proliferation (14). Taking

this into account, we decided to evaluate the expression of SSP genes in leukemic blasts to determine whether they have altered expression in AML patients.

The results of our study indicated no significant changes in the expression of PHGDH as the first SSP enzyme (fold change = 0.86, $P=0.290$) and decreased expression of PSAT1 (fold change = 0.10, $P=0.002$) and PSPH (fold change = 0.35, $P=0.026$), the second and third enzymes in serine biosynthesis pathway, respectively. However, a positive and statistically significant correlation was observed between these three genes in leukemic blasts of our patients. It is supposed that the down-regulation of any of these key enzymes should result in SSP suppression as a pivotal pathway for serine generation (15).

Some cancer cells exhibit SSP enzyme amplification, and their survival is contingent upon the sustained expression of these enzymes, even when serine is externally supplied. Cancer cells that do not have SSP amplification are more likely to rely on exogenous serine to support their optimal growth (7). Previous studies have demonstrated that normal hematopoietic and leukemic cells growth will be inhibited in the absence of serine (10). Therefore,

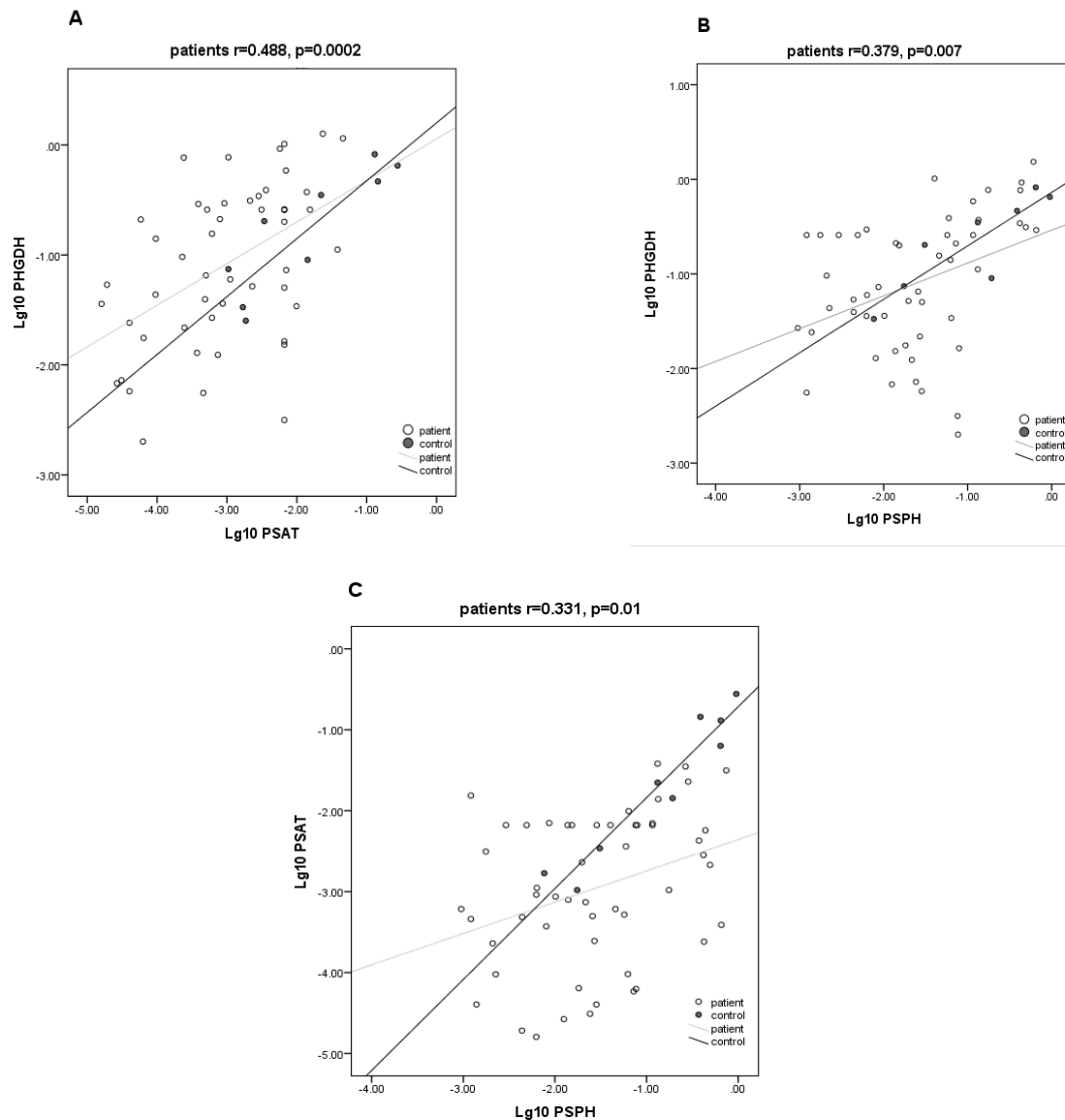


Figure 5. Pearson test was applied to show the correlation between PHGDH, PSAT, and PSPH expression levels. There were significant and positive correlations between the expression of (A) PHGDH with PSAT ($r=0.488$, $P=0.0002$), (B) PHGDH with PSPH ($r=0.379$, $P=0.007$), and (C) PSAT1 with PSPH ($r=0.331$, $P=0.01$) in AML patients

our findings of SSP genes down-regulation seem to be inconsistent with what we expect from malignant cells. Recent research on AML cells has demonstrated that FLT3-ITD is critically involved in modulating serine metabolism through PHGDH and PSAT1 overexpression. Also, these cells are sensitive to PHGDH inhibition even when exogenous serine is available. Actually, FLT3-ITD mutation has been recognized in 30% of all AML (16). It suggests that the upregulation of SSP genes may not consistently confer survival and proliferative advantages in all AML cell populations. This pathway likely has a tumor suppressive function in hematologic malignancies so myeloid blasts opt the available serine. On the other hand, Various investigations on solid tumors have shown that overexpression of SSP genes exerts oncogenic effects independently of serine production (17). In this regard, increased expression of PHGDH has been demonstrated

in cervical adenocarcinoma, glioma, colorectal and pancreatic cancer (17-20). Furthermore, there is evidence of elevated PSAT1 expression in colon cancer, esophageal squamous cell carcinoma, and non-small cell lung cancer (NSCLC) (9, 21, 22). In the study conducted by Noh et al. (2014), breast cancer tissue from triple-negative breast cancer subtypes displayed increased expression of PHGDH and PSPH (23). As mentioned, previous studies have demonstrated that solid tumors benefit greatly from the overexpression of SSP genes owing to high levels of α -KG and other oncogenic products of this pathway, such as D-2-hydroxyglutarate (D-2HG); while these events may arise from numerous gene mutations in leukemic cells (24).

Furthermore, some studies indicate a complexity in the pattern of SSP expression in certain situations. For example, the study by Regan JD et al. on normal

bone marrow and chronic granulocytic leukemia cells demonstrated that these cells have minimal ability to synthesize C14-serine from C14-glucose (10). Moreover, Iwamoto et al reported the absence and low PHGDH expression in leukemic and normal CD34+ cells, respectively, while this gene showed overexpression in bone marrow mesenchymal cells, and showed that these cells act as supportive tissues which provide the required serine for normal and leukemic hematopoietic cells (25). It is hypothesized that, although serine has a critical role in tumor growth, malignant myeloid cells do not tend to produce serine through SSP upregulation. Instead, they benefit greatly from the serine obtained from alternative sources. Therefore, upregulation of SSP genes in stromal cells, destruction of intracellular proteins through autophagy, and dietary serine are possible sources of supplying serine for malignant myeloid cells.

Last but not least, SSP gene expression has shown significant differences between males and females in our study. Sex differences in the serine metabolism pathway have been displayed in solid tumors in recent investigations. In 2022, an investigation about de novo serine synthesis by Sponagel et al, demonstrated that serine amino acid in male NSCLC cells is produced more than in female cells (26). Differences in expression of metabolic pathway-related genes in males and females highlight their crucial role in treatment response. Therefore, evaluation of SSP considering sex and gene expression in AML patients may help improve future therapeutic approaches.

Conclusion

The SSP likely mimics a tumor-suppressive function in hematologic malignancies, so myeloid blasts opt for the available serine. While the mentioned investigations have suggested that SSP genes are promising targets in carcinomas, these genes may not be suitable targets for direct inhibition in leukemia. However, further investigations are required to determine the role of dietary serine, expression of SSP genes in stromal cells, or genes involved in downstream pathways in AML development, which could provide a favorable perspective on AML therapeutic approaches.

Acknowledgments

We have deep gratitude towards the Department of Hematology and Blood Banking, Shahid Beheshti University of Medical Sciences, and the HSCT Research Center of Taleghani Hospital.

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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

Written consent was obtained from all participants, including patient and control individuals. The Local Ethics Committee approved the study (Ethical code: IR.SBMU.RETECH.REC.1397.604).

Funding

This is a self-funded study. This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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