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The Impact of Variations in the Expression of *Dicer* on Pediatric Acute Lymphoblastic Leukemia

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Abstract

Background & Objective: *Dicer* a member of the RNase III endonucleases has a crucial function in the development of miRNAs that affects gene expression in different kinds of cancers. The present research focused on examining the expression level of *Dicer* and its relation with clinicopathological features in children with Acute Lymphoblastic Leukemia (ALL) among the population in the northwest region of Iran.
Materials & Methods: In a case-control study, 140 samples (70 patients and 70 healthy controls of similar age and sex rates) from 2019 to 2021 were included in the *Dicer* mRNA expression levels assessment. Quantitative Real-Time PCR analyses were utilized to determine expression levels of *Dicer* in samples and the demographic and clinicopathologic features and the relationship of these variables were evaluated.
Results: Average *Dicer* expression □ct values were 2.8267 and up-regulated compared to healthy samples (P=0.000). No significant relationships have been found among gene expression, demographical and clinicopathological parameters. Also, demographical and clinicopathological factors were not correlated with the mRNA expression level of the gene except age (r=0.148, P=0.001).
Conclusion: The current research shows that the expression of *Dicer* is significantly up-regulated in ALL patients, which suggests that it could have a vital function in ALL pathology. It will also theoretically be seen in the potential as a new intervention objective for ALL cases.

Keywords: RNase III endonucleases, *Dicer* Gene, pediatric acute lymphocytic leukemia, Gene Expression

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Introduction

Leukemia is a malignancy of the hematopoietic cell population that includes diverse and biologically distinct subgroups (1). Acute lymphoblastic leukemia (ALL) is a malignant lymphoid and one of the four major types of leukemia that are common in kids under the age of 16, with a maximum prevalence between the ages of 2 and 5 (2). For children aged 2 to 5 years, the survival rate is about 90 percent. Even so the odds of post-therapeutic success were lower for those below 1 year of age and those above 10 years of age (3). ALL is defined by clonal multiplication and aggregation of growth factors displaying early phase cell markers of

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lymphoid development with features of either B-cell or T-cell engagement (4). In ALL, primitive B and T cells grow and rise in numbers in an unchecked manner. They limit the number of other regular blood cells and eventually induce multiple diseases in the infected person (5). Treatment options contributing to the rise of ALL include environmental, genetic, and infectious variables. Identifying risk factors for ALL is a major step in reducing the total burden of disease (6). MicroRNAs (miRNAs) are a class of small non-coding RNAs (~22 nucleotides) that are associated with chromatin rebuilding, genome readjusts, tissue biogenesis, stem cell conservation, and control of gene expression by manipulating miRNAs and either causing translational suppression or degradation of RNA (7, 8). Incorrect expression or control of miRNA can lead to cancer. This will also illustrate the role of miRNA as an oncogene or tumor suppressor (9). Several miRNA terms such as miRNA-18a, miRNA-19a, miRNA-19b1, miRNA-20a, miRNA-21, miRNA-92-1, miRNA-99a, miRNA-100, miRNA-142, miRNA-150, miRNA-181a, miRNA-181b and miRNA-223 have been indicated to modify at any point of ALL (10). It can also be suggested that improvements in the expression of genes participating in the biogenetic mechanism of miRNAs can play a critical role in ALL and can be deemed a contender for their development or growth. Also, miRNAs are expressed uniquely in a distinct lymphopoiesis stage and affect the maturation stage of lymphoid precursors (1).

MiRNAs are generated by a step-by-step process mechanism driven by some regulators enzymes, like *Dicer* (11). *Dicer*, a ~ 230 KDa protein, is a member of the RNase III endonucleases and a cytoplasmic endonuclease that have crucial functions in the development of miRNAs and affect gene expression by causing different miRNA molecules to be disrupted (6,12). Prime miRNA breaks into a small duplex RNA substrate called pre-miRNAs in the nucleus and pre-miRNAs are transferred to the cytoplasm where *Dicer* split them into roughly 22 nucleotides mature double-stranded miRNA (8).

It has revealed that any significant alteration in the expression of *Dicer* could contribute to the pathogenesis of certain cancers. Different studies have paid to the role of *Dicer* in numerous kinds of cancers: prostate, colorectal, lung, cervix, salivary gland, ovarian, esophageal, myeloma, AGS, and HepG2 cancer cell lines, bladder (7, 12-23), but as a web-based search (all available databases until the date of sending the article by *Dicer*, ALL, pediatric acute lymphocytic leukemia and expression as keywords) there are just two papers on *Dicer* expression in pediatric ALL (3, 6) that results from them have been different and this shows the significance of further investigations to attain precise and conclusive results.

Materials and Methods

In the present research, we focused on examining the expression level of *Dicer* and its relation with clinicopathological features in children with ALL among the population in the northwest region of Iran.

Patient characteristics

In a case-control study, at Shahid Ghazi Tabatabaie Hospitals, Tabriz University of Medical Sciences, 70 children aged 11 months to 13 years were diagnosed as new cases of ALL and 70 healthy controls in similar age and sex rates, from 2019 to 2021. Healthy control volunteers did not have any disease neither themselves nor their immediate family members and were tested by Cell Counter (Sysmex (K 1000), Japan) and peripheral smears (all normal). The accuracy of the diagnosis was confirmed by the use of immunological testing (flow cytometry), complete blood count, and monitoring of the peripheral blood by a hematologist-oncologist (according to the legal standards of the global oncology community).

Patients who met the following criteria were excluded:

1. More than 14 years of age
2. Existence of other hematological diseases,

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the background of other malignancies, or recurrence of ALL
3. Those on chemotherapy or radiotherapy
Diagnosis and description of the disease were calculated based on the EGIL (European Group of Immunophenotyping Leukemia) as pro-B cell, pre-B cell, B-cell, T-cell, and mixed ALL (24) and FAB (French-American-British classification) as L1, L2, and L3 (25). Patient age and baseline white blood cell (WBC) counts are a predictor of outcome, as older patients and/or patients with higher white blood cell counts had worse outcomes than younger patients and/or those with lower white blood cell counts. These variables are used on the basis of NCI-Rome (National Cancer Institute-Rome) criteria to classify patients into 2 groups: standard risk (age 1-9.99 years and WBC<$50*10^9$/L) and high risk (aged≥10 and aged<1 years and/or WBC>$50*10^9$/L) subgroups (26).

Sample Collection

Approximately, 3 mL of peripheral blood was collected from all patients and controls under sterile conditions with written informed consent by the parents of the patients and the controls.

RNA Extraction and cDNA Synthesis

RNA was extracted from the whole blood, RNX-Plus solution (Sinaclon, Iran) was used for a collection of complete RNA from a 250 µL blood sample as instructed by the producer, and purity was assessed by A260/280 ratio (>1.8) using the Nanodrop (ND-1000, Thermo Fisher Scientific, USA). The complete RNA was transcribed in reverse and cDNA was prepared using Revert Aid first-strand cDNA synthesis kit (Thermo Fisher Scientific, USA) following the instruction of the manufacturer.

Quantitative Real-Time PCR

Primers that were included in this study were pre-designed by Gene Runner software and specificity of them was distinctive by the Basic Local Alignment Search Tool (BLAST). In our investigation we used the primers and probes sequences (Table 1) for the *Dicer*, *ABL*, and *GAPDH* as housekeeping genes.

Table1. Primers and probes were used for real-time PCR gene expression of *Dicer* gene

Target	Sequences	Amplicon size (bp)	Melting Temperature (°C)
Dicer -F	5′- CCCCACTTTAGAGCCCTGTG - 3′	128	59.23
Dicer -R	5′- GCCTCCCCAGTCCTTTACAC - 3′		59.97
Dicer -P	5′- TGGGGTGTGGTTGTGCCCTG - 3′		60.32
GAPDH-F	5′-GAAAGCCTGCCGGTGACTAA- 3′	150	60.00
GAPDH-R	5′-CTGCGCTCCTGCCTCGATGG- 3′		60.31
GAPDH-P	5′-AGGAAAAGCATCACCCGGAG- 3′		59.30
ABL-F	5′- AGGACTCTCGTCTCATGCCT - 3′	107	60.60
ABL-R	5′- CAGCTTCAGTGCAAGTGCTG - 3′		59.39
ABL-P	5′- TCCAGCTGCCCTAACCGCAGA - 3′		59.09

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The mRNA expression level of *Dicer*, *GAPDH*, and *ABL* as a housekeeping gene was measured by qRT-PCR analysis using Taq-man universal PCR mix (Thermo Fisher Scientific, USA) according to the manufacturer's instruction, whose genes expression was quantified by Taq-man Gene Expression Assays (Thermo Fisher Scientific, USA). Outcomes were assessed on a 7500 Real-time PCR system (Applied Biosystem, USA). The PCR cycling began with an initial step of 95ºC for 10 min followed by 40 cycles of 95 ºC for 15 sec and 60 ºC for 30 sec. Reactions were performed with three replications and each experiment included a negative influence without the template.

Statistical analysis

Dicer expression levels were standardized to the arithmetic mean of endogenous housekeeping genes *GAPDH* and *ABL*. The data were evaluated using the $-\Delta\Delta C^2$ tct approach (27).

An independent T-Test was conducted to assess the significant difference in the average improvement of gene expression in cases and healthy samples. The combination of demographic and clinicopathological variables to *Dicer* expression levels was evaluated using the Fisher's Exact Test, the Independent T-Test, and the Chi-Square Test. Pearson Correlation Coefficient has been used to correlate demographic and clinicopathologic variables with gene expression. In categorical data, the average value has been used as a threshold, and the scale data were expressed as a mean ± standard mean error. Statistical comparisons are made by SPSS (version 26, IBM, USA) and statistically significant results of $p<0.001$ were found.

Results

In this study, 70 patients with ALL and 70 healthy controls have been examined. No attempt has been spared to identify some alteration in the expression of *Dicer* in patients. The mean age of the control group was 5.74±2.46 (range 1-13 years) and the case group was 6.46±3.15 (range 11 months to 13 years). A total of 61.4% of the case and 50% of control were female and the remainders were male. There is no significant difference between age and sex in patients and controls ($p>0.001$) and healthy control was age and sex-matched with patients. A substantial amount of patients (61.43%) had a WBC count range of 35-11*10^9/L, 71.43% of them had hemoglobin (HB) amount less than 12gr/dL, and 75.71% of them had platelets (PLT) count range 140-450*10^9/L. A total of 58.58% of patients had blast cells less than 80% and 41.42% of them had blast cells above or equal to 80%. According to EGIL classification, patient samples lead to pro-B cell, pre-B cell, B-cell, T-cell, and mixed ALL levels with the highest level of the pre-B cell (afflicting 41.43% of patients). According to the FAB classification, the highest level of the disease was L1 (68.57%) and there was no ALL-L3. Taking into account the prognosis and risk factors, 78.57% of patients are at standard risk, and the rest are at high risk (Table 2).

Table2. Demographic and Clinicopathological data of ALL patients and their Relationship with *Dicer* expression level

Parameter	Value (N=70)		Gene Expression			
	Mean +SD (Min-Max)	N (%)	Mean ±SD (Min-Max)	low	high	p-value
Age (year)	6.46±3.15, 0.917±13					

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Age (year)	6.46±3.15, 0.917-13					
<1		2 (2.86%)	2.4500±0.00 (2.45)	0	2	0.004
1-9.99		55 (78.57%)	3.1219±1.23 (-0.57-4.42)	7	48	
10≤		13 (18.57%)	1.8626±1.52 (-0.57-4.23)	7	6	
Sex						
Female		43 (61.42%)	2.8651±1.47 (-0.57-4.42)	8	35	0.510
male		27 (38.58%)	2.6598±1.12 (-0.57-4.02)	6	21	
WBC (10 ^{9}/L)	5.40±3.71, 0.86-22.8					
<3.5		24 (34.28%)	2.6824±1.39 (-0.57-4.42)	6	18	
3.5-11		43 (61.43%)	2.7421±1.22 (-0.57-4.42)	8	35	0.612
11>		3 (4.29%)	4.0154±0.63 (3.23-4.29)	0	3	
HB (gr/dL)	10.98±1.43, 7.9-13.7					
<12		50 (71.43%)	2.6531±1.43 (-0.57-4.42)	18	32	
12-17.5		20 (28.57%)	2.8350±1.23 (-0.57-4.02)	7	13	0.502[a]
>17.5		0	0	0	0	
PLT (10 ^{9}/L)	246.37±122.47, 14-506					

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<140	12 (17.15%)	3.1002±1.29 (-0.57-4.42)	1	11	
140-450	53 (75.71%)	2.7998±1.41 (-0.57-4.02)	12	41	0.496
450>	5 (7.14%)	2.8936±0.87 (1.19-3.51)	1	4	
Blast Cells (%)					
% Blast <80	41 (58.58%)	2.5687±0.84 (1.62-3.74)	19	22	0.401
% Blast ≥80	29 (41.42%)	2.3012±0.90 (1.53-3.35)	11	18	
EGIL sub classification					
Pre-B cell ALL	29 (41.43%)	2.5623±1.40 (-0.57-4.02)	9	20	0.431
B-cell ALL	8 (11.43%)	2.8612±0.78 (1.65-3.51)	1	7	
T-cell ALL	21 (30%)	3.0358±0.91 (1.24-4.42)	1	7	
Pro-B cell ALL	8 (11.43%)	3.4569±1.84 (-0.57-4.02)	2	19	
Pro-B cell ALL					
Mixed ALL	4 (5.71%)	2.2397±2.64 (-0.57-4.32)	1	3	
FAB sub classification					
L1	49 (68.57%)	2.2564±0.56 (1.84-2.98)	16	33	0.324
L2	21 (31.43%)	2.4982±0.51(1.36-3.74)	9	12	

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L3	0	0	0	0	
NCI/Rome criteria sub classification					
Standard risk	55 (78.57%)	3.2039±1.17 (-0.57-4.42)	18	37	0.532
High risk	15 (21.43%)	1.8974±1.35 (-0.57-4.02)	7	8	

P-value: Chi-Square Test, [a] Fisher's Exact Test

The expression of *Dicer* was quantities by qRT-PCR in ALL patients and healthy subjects and standardized to an arithmetic mean of *GAPDH* and *ABL* mRNA levels (cases: 20.4221 ± 0.75 and controls: 19.7293 ±0.38). *Dicer* expressions were explored in patients (mean 2.8267±1.27, min -0.57, max 4.42) and compared with control (mean 1.9783±1.26, min -0.79, max 5.12). The expression level (Chart 1) of *Dicer* mRNA was substantially (p=0.000) higher in ALL patients relative to the healthy sample.

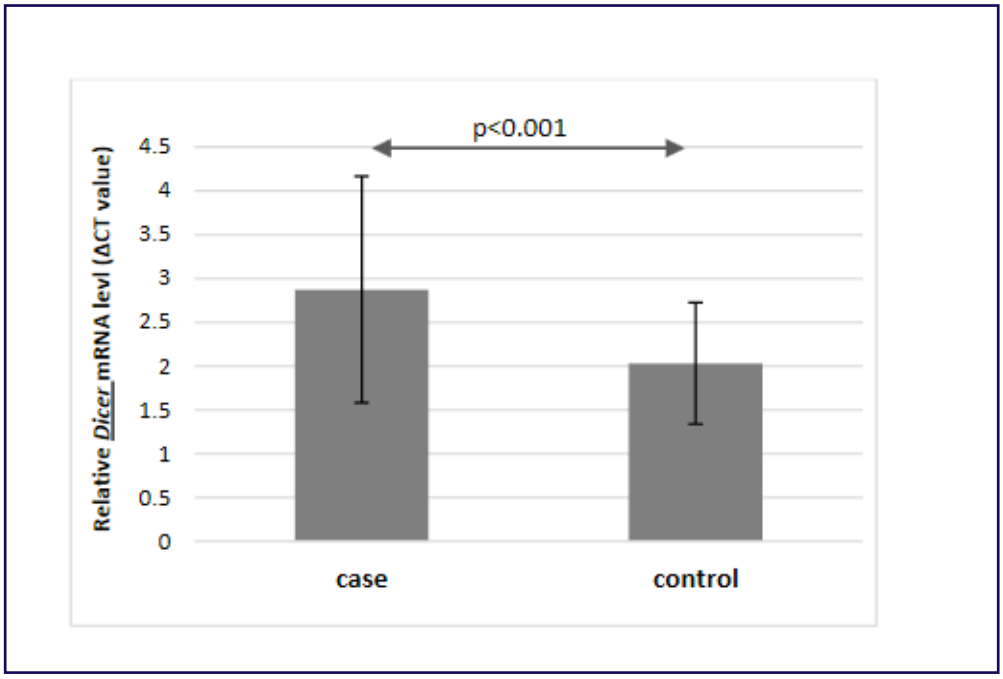

Chart 1. Relative *Dicer* expression in the ALL patients and control group

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The mRNA expressions of *Dicer* have been tested in ALL patients for differences in demographic and clinicopathological specifications to examine the biological function of *Dicer* in ALL. Specific investigations were classified in high and low *Dicer* expression classes based on the average expression $-\Delta\Delta C^2$. No substantial variations in the demographic features (age and sex) of *Dicer* expression have been found in the cases ($p>0.001$). It was also found that *Dicer* expressions did not statistically differ by WBC, HB, and PLT amounts. The *Dicer* expression was also shown to be different between patients in the group of blast cells <80% and ≥80% but this difference was not significant. A significant increase in mRNA expression of *Dicer* was not observed between Pre-B cell, B-cell, T- cell, pre-B cell, and mixed ALL. However, *Dicer* expression was higher in L2 than in L1 but this increased gene expression was not statistically significant ($P> 0.001$). No significant increase in mRNA expression of *Dicer* was observed between standard and high-risk groups too (Table 2). It was found that the clinical and demographic parameters had no significant effect on the expression level of *Dicer* in this study.

In correlation analysis (Table 3) demographical and clinicopathological factors in patients did not associate with the mRNA expression level of the gene except *Dicer* and age there was a negative correlation between the increased expression level of *Dicer* and age ($p=0.001$, $R=0.148$).

Discussion

ALL accounts for %85 of leukemia in childhood (1). Poor prognosis and resistance toward treatment are the key characteristics that represent some cases of ALL as incurable cancer (2).

MiRNA processing is such a good mechanism for determining miRNA biosynthesis. MiRNA is a classification of epigenetics modification with different types of cancer by researchers and is a new trend to gain a bigger insight into the etiopathology of these diseases. Information suggests that various irregular expressions of miRNA may contribute to ALL, e.g. in the analysis of Zhang et al (17), up to 171 miRNA, is communicated differently across ALL patients and stable contributors. Changes in the role of miRNAs can modify the expression of multiple genes, such as genes involved with the evolution of ALL (28). In miRNA biosynthesis, some molecules including *Dicer* have an effective role (29). *Dicer* is one of the main components of the miRNA loading system. Production of mature endogenic interference RNA requires a series of events invariably associated with the functions of *Dicer* and other components of the miRNA loading complex (6). Lee et al. showed that the sequence of miRNA precursors and maturity is decreased in cells with silent expression of *Dicer* (30). Bernstein et al. documented that *Dicer's* failure in mice interferes with embryonic stem-cell development which is deadly in developmental stages (31).

A web-based search revealed that there are just two papers on *Dicer* expression, as shown by Farzaneh et al., in the Fars province of Iran, *Dicer* gene expression in ALL patients (18 cases, 1 to 20 years old) significantly decreased compared with control (10 people) (6), It was stated that an increased expression of *Dicer* in 25 patients afflicted with ALL and 25 healthy subjects as control by Piroozian et al, in Hormozgan province of Iran (3). Therefore, this study is one of the limited literatures on *Dicer* expression, especially in children with ALL hematopoietic cancer.

Dicer is the major element of the biogenesis and adjustment of miRNA, thus, its gene expression levels are reported in different cancers. Up-regulation of *Dicer* in colorectal carcinoma was confirmed to be correlated as a good indicator of poor prognosis (15). Moreover, increased expression of *Dicer* in prostate adenocarcinoma is associated with aggressive cancer features (13), up-regulation of *Dicer* in precursor damage of lung adenocarcinomas (14), and up-regulation of *Dicer* in patients with normal results in non-small cell lung cancer are positive predictive markers, (12). Similarly, it is suggested that *Dicer* may be complicit in colorectal

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carcinomas pathobiology and may play a part in these tumors' progression to an advanced stage (7) and it is revealed as an improved expression of components of miRNA processing machines such as *Dicer* in salivary gland pleomorphic adenomas (17). A histogram of the expression of *Dicer*l revealed a confidence interval in esophageal cancer with two major peaks at log 2 values (20). Also, colorectal adenocarcinoma was investigated, and identified *Dicer* mRNA expression levels to be substantially elevated in carcinomatous tissue relative to non-neoplastic tissue (18). *Dicer* has also been seen overexpression of cervical squamous cell carcinomas (16); furthermore, the up-regulated expression of *Dicer* is shown to be connected with progressed tumor grade in serous ovarian carcinoma and indicates a role for this molecule in cancer development (19). The analyzed *Dicer* expression levels in multiple myeloma patients showed that the expression levels in monoclonal gammopathies were considerably higher (21) and it has been established that *Dicer* expression is up-regulated in AGS and HepG2 cancer cell lines (22). It was also seen in patients with urothelial carcinoma of the bladder that Dicer up-regulated (23). In this study, we examined whether *Dicer* was expressed in ALL patients. At this level, this ribonuclease is expressed in all of the samples tested. Also, we observed that *Dicer* mRNA was also expressed in the normal sample. Our findings indicate significant up-regulation of *Dicer's* levels of mRNA expression in ALL patients relative to the normal sample that provides new evidence for plausible involvement of up-regulated miRNA in the ALL development. It seems that because *Dicer* is important for producing mature miRNA, higher levels of *Dicer* increase multiple miRNA species expression in ALL. The inverse result of decreased *Dicer* on miRNA was identified in lung cancer at which *Dicer* levels reduced corresponded to a reduction in let-7 microRNA (32). A previous study of microarrays showed that miRNA plays a key role in many of the load factors linked to cancer and cell cycle regulation (33). Up-regulation of miRNA may contribute to the activation of the TSG (tumor suppressor gene); this is active in cell proliferation and division by leading to ALL of the development (34). Among the demographical and clinicopathological characteristics of ALL patients, all parameters were very similar to the healthy donors and these factors were not affected and correlated with the expression of *Dicer* except age which significantly correlated with the expression of *Dicer*. Reports that have been published about the dependence of *Dicer* expression with clinicopathological factors in cancers were the inspiration for this research; Wu et al. reported that the expression level of *Dicer* was not related to the clinical feature in hepatocellular carcinoma (35). Kim et al. found that there was no association between the *Dicer* mRNA expression levels and any clinical factor in colorectal adenocarcinoma (18). Likewise, Merritt et al. studied the correlation of clinicopathological features towards the level of *Dicer* mRNA in ovarian cancer and found no substantial interaction between them (36). Also, Vaksman et al. (20) stated that *Dicer* mRNA and protein content were not linked to the clinicopathologic parameter for ovarian cancer. Moreover, Avery-kiejda et al. documented no association between *Dicer's* expressions and clinical factors in triple-negative breast cancer (8).

However, our findings as a preliminary investigation revealed that the *Dicer* gene up-regulated in pediatric ALL patients. There are several limitations in our study. The number of sample size is not enough for subgroup analysis. This small number may have led to the result that *Dicer* gene expression level had no significant impact on pathogenesis. However, their findings reinforce a significant appearance of Dicer in pathogenesis of ALL and suggested that the cancer specific functions of this gene in tumorigenesis were assessed in future investigations. In addition, more investigation is needed to clarify the clinical

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significance of the *Dicer* gene expression level in ALL. In addition, the molecular mechanisms of the *Dicer* gene in tumor progression and development need to be determined in the future work.

Conclusions

Dicer expression at mRNA levels was increased in a large number of *ALL* patients compared with healthy control. Dysregulation of the factors involved in miRNA biogenesis has been presumed to influence the level of miRNAs. This abnormal control of miRNA biosynthesis can lead to disruptions in other cell processes, especially in favor of cancerous cells. Overexpression of such elements may appear to be involved in the growth and prevalence of cancer through cell cycle dysfunction, tumorigenesis control, and metastases. It became evident that variation in the transcriptional level of such elements implicated at miRNA biosynthesis associated with the development and growth of such a disease may be regarded as a potential predictor for the development of ALL or diagnostic indicator.

Data Availability Statement

All data related to this research have been included in the manuscript.

Ethical Approval

This study complies with ethical approval from the Ethics Committee of Tabriz University of Medical Science (IR.TBZMED.REC.1398.732, 2019).

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Conflict of interest

The authors declare that they have no conflicts of interest.

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