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NRF2 Expression at T-All Diagnosis Could Predict Response to Induction Therapy

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ABSTRACT

Background: The nuclear factor erythroid 2- related factor 2 (NRF2), has a significant impact on cancer chemoresistance. There is limited knowledge regarding its effect on the response of T cell acute lymphoblastic leukemia (T-ALL) to therapy. The objective of this study was to examine the effect of NRF2 expression on the induction remission response in T-ALL patients.

Patients and Methods: This study involved 50 patients diagnosed with T-ALL and 20 controls subjects. The expression levels of NRF2 were assessed using real-time PCR at the time of diagnosis (day 0), on day 28 following induction chemotherapy, and in the control group.

Results: The baseline expression levels of NRF2 in the T-ALL cohort at the time of diagnosis (day 0) [median 7.7 (range :6.8-10.2)] were markedly increased as compared to those observed in the T-ALL group on day 28 [(median:4.4 (range 3.2-9.1)], as well as in the normal control group [(median: 3.2 (range :2.7-4.9)] ($P<0.0001$ for all). A significant correlation was identified between NRF2 expression and BCL2 expression at the time of T-ALL diagnosis indicating that the expression of NRF2 is linked to the burden of blast cells in T-ALL. A high incidence of induction remission failure was noted among the subgroup of T-ALL patients exhibiting NRF2 overexpression. Furthermore, multivariate analysis indicated that increased NRF2 expression at diagnosis serves as an independent predictor (OR: 17.166 (2.587-31.901) of the induction remission failure.

Conclusion, our research indicates that elevated NRF2 expression at the time of T-ALL diagnosis may serve as a predictor of inadequate response to induction chemotherapy, primarily due to the upregulation of BCL2 expression.

Keywords: T-ALL, NRF2, BCL2, induction remission.

INTRODUCTION

Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that is encoded by the NFE2L2 gene. It functions as a primary regulator of cellular antioxidant defenses by enhancing the transcription of genes that possess antioxidant response elements (AREs). These elements play a crucial role in protecting cells from various oxidative damage caused by both external and internal factors [1-3].

The function of NRF2 in cancer exhibits a bimodal nature, presenting either advantageous or harmful effects on cancer cells, contingent upon the stage of the tumor and the persistence of signaling. In the initial phases, the temporary activation of NRF2 antioxidant properties appears crucial for preventing the development of premalignant tumors, mitigating DNA damage, and addressing early cancer mutations[4]. On the other hand, during advanced stages, prolonged hyperactivation of NRF2 could establish an environment that promotes the survival of tumor cells by protecting them from excessive oxidative stress, chemotherapy drugs, or radiation treatment[5].

Furthermore, NRF2 plays a role in the metabolic reprogramming associated with cancer, directing metabolic intermediates into the Warburg and pentose phosphate pathways to support proliferative growth and uphold redox balance [6]. The extended activation of NRF2 signaling within tumor cells results from multiple mechanisms, such as somatic mutations in NFE2L2 or KEAP1, skipping of exon 2 in NFE2L2, reduced expression of KEAP1 due to promoter hypermethylation, and transcriptional activation of the NFE2L2 gene[7]. Recent research has revealed increased levels of NRF2 in various solid tumor types, including head and neck, gastric, breast, gallbladder, and ovarian cancers [8].

NRF2 plays a crucial role in inhibiting apoptosis by promoting the expression of BCL-2 and BCL-Xl. Additionally, NRF2 obstructs the intracellular apoptosis pathway by preventing the release of cytochrome C from mitochondria[9]. Research investigating the relationship between NRF2 and apoptosis indicates that following exposure to cytotoxic agents such as cyclophosphamide or etoposide, NRF2 diminishes both intracellular and extracellular apoptosis pathways by inhibiting the activation of caspase-7 and caspase-3[10]. Consequently, the upregulation of BCL-2 enhances NRF2 activity. The depletion of NRF2 through siRNA in periodontal ligament stem cells (PSCs) results in an increase in caspase 3 and 9, as well as elevated levels of Bax at both the protein and mRNA levels[11].

Multiple clinical studies have shown that the buildup of NRF2 is associated with poor prognoses in a range of tumors, such as those affecting the brain, lung, esophagus, breast, liver, bladder, pancreas, cervix, melanoma, ovary, stomach, and colon [12-14]. This suggests that NRF2 and its downstream effectors may serve as

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prognostic indicators across a broad spectrum of cancers. In the context of hematological malignancies, the overexpression of NRF2 has been linked to drug resistance and the progression of the disease[15,16].

T-cell acute lymphoblastic leukemia (T-ALL) represents the malignant transformation of T-cell progenitors at various stages of differentiation [17]. Despite ongoing research aimed at unraveling the molecular intricacies of T-ALL, current treatment strategies primarily rely on chemotherapeutic regimens, which may be succeeded by hematopoietic stem cell transplantation for patients classified as high-risk [18]. These treatment approaches yield satisfactory initial complete response rates; however, approximately 40% of adult patients and 15% of pediatric patients with T-ALL experience relapse. Regrettably, individuals who either relapse or fail to respond to first-line therapies face significantly poor prognoses, with cure rates plummeting to 7% [7].

Studies have shown that the overexpression of NRF2 provides protection to tumor cells against cytotoxic effects, inhibits apoptosis, and contributes to resistance against tumor cell therapies [8,9,19]. **Lin *et al.*[20]** discovered that among patients with high-risk myelodysplastic syndrome (MDS), the expression level of NRF2 in bone marrow cells was 5.3 times higher compared to those with low-risk MDS, while the response rate to cytarabine treatment ranged from 20% to 30%. Limited research has been conducted on the role of NRF2 in influencing the response to induction chemotherapy in patients with hematopoietic malignancies, particularly those with T-cell acute lymphoblastic leukemia (T-ALL). Consequently, our aim was to examine the effect of NRF2 expression on the induction remission response in T-ALL patients.

PATIENTS AND METHODS

Patients

The study included 50 T-cell acute lymphoblastic leukemia patients (28 males, 22 females) attending Mansoura University Oncology Center before start of therapy; their median age was 12 years (age range 4-16 years) of matched sex and age. The diagnosis of T-ALL was based on blood counts, blood smear, bone marrow smear and confirmed by immunophenotyping.

Inclusion criteria: Patients who were under 18 years of age, recently been diagnosed with T-ALL.

Exclusion criteria: Secondary leukemia, the presence of other malignancies, patients undergoing treatment for T-ALL.

Methods

All clinical data were recorded including hemoglobin, platelets, WBCs, blood blast cells count, and bone marrow blast cells count.

NRF2 expression was measured in the bone marrow samples using real time PCR at 2 points disease course: diagnosis, after induction of remission, as well as in control group.

The treatment regimen was founded on the ALL-BFM 90 protocol; it included induction therapy with prednisone, vincristine, daunorubicin, L-asparaginase, and methotrexate, succeeded by consolidation therapy utilizing 6-mercaptopurine and methotrexate [21]. A patient with Philadelphia chromosome positive T-ALL was administered imatinib (340 mg/m2/day, with a maximum of 400 mg/day), integrating all phases of chemotherapy until the conclusion of maintenance chemotherapy.

Bone marrow samples were obtained from patients diagnosed with de-novo T-ALL, as well as from patients who were referred for bone marrow evaluation and confirmed to be hematologically free (control group). Bone marrow mononuclear cells were separated using Ficoll density gradient centrifugation.

Remission of induction: This was tested by BM aspiration at day 28. Complete hematological remission was addressed when blast cells count <5%. Minimal residual disease (MRD) detection was applied to confirm induction remission response.

NRF2 expression quantification

RNA extraction and real time PCR

Bone marrow samples was obtained from the population of patients and controls; A total of 2 ml of BM sample from the subjects was introduced into 15 ml Falcon tubes that contained 100 µl of the antagonist EDTA at a concentration of 10%. Subsequently, total RNA was extracted utilizing an RNA extraction kit (Sigma St. Louis, MO, USA) in accordance with the manufacturer's instructions. The quality and quantity of the extracted RNA were assessed through 1% agarose gel electrophoresis, and the total RNA concentration was determined using a BioPhotometer (Eppendorf AG, Hamburg, Germany). The quantitative real-time PCR method utilized SYBR green technology (Tian Gen Biotech, China) on cDNA that was synthesized from the reverse transcription of isolated RNA. After preamplification at 95°C for 2 minutes, the PCR reactions were performed for 45 cycles (95°C for 15 seconds, 60°C for 10 seconds, and 72°C for 10 seconds) using a 384-well Light Cycler 480 (Roche; USA). The relative expression levels were quantified using the 2-ΔΔCT method, with mRNA expression normalized to β-actin levels. NRF2 primers F- 5`-TTCCCGGTCACATCGAGAG-3`; R- 5-TCCTGTTGCATACCGTCTAAATC-3`. Beta actin primers were forward: 5`-CACCATTGGCAATGAGCGGTTC-3`; R: 5`-AGGTCTTTGCGGATGTCCACGT- 3`

BCL2 expression

RT-qPCR

Real-time quantitative PCR (RT-qPCR) was conducted to analyze BCL2 mRNA levels utilizing AceQ qPCR SYBR Green Master. The primers for BCL2 expression included 5′-CCCTGGTGGACAACATCG-3′ as the forward primer and 5′-CAGGAGAAATCAAACAGAGGC-3′ as the reverse primer. The housekeeping gene beta actin was assessed through RT-qPCR with 2 × SYBR Green PCR Mix (Tian Gen Biotech, China). The relative levels of BCL2 mRNA were determined using the 2-ΔΔCT method. beta Actin (ACTB) Human qPCR primers were forward: 5`-CACCATTGGCAATGAGCGGTTC-3`; R: 5`-AGGTCTTTGCGGATGTCCACGT- 3`.

Ethical considerations

The current study was reviewed and approved by the local Ethics Committees at Mansoura Faculty of Medicine, Mansoura University. Written informed consents were taken from the parents of children participating in the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

The information was examined, coded, and tabulated with the help of IBM's Statistical Software for the Social Sciences (2017 release) (version 25.0 of IBM SPSS Statistics for Windows, IBM Corp, Armonk, New York). The data underwent evaluation to ascertain whether they were parametric or non-parametric, which informed the selection of the appropriate statistical test. Comparisons of NRF2 expression at the stages of diagnosis, remission, and relapse were conducted using the Student's t-test. Cox regression analysis was performed to identify independent factors that could predict the induction of remission response. The ROC curve was employed to establish the optimal cutoff value of NRF2 expression levels that could forecast the induction of remission response. Additionally, a correlation coefficient test was utilized to evaluate the relationship between NRF2 expression and BCL2 expression at the time of T-ALL diagnosis. P value <0.05 was considered significant.

RESULTS

T-ALL patients characteristics at diagnosis are shown in table 1.

Table 1. Patients' characteristics among studied T-ALL group.

T-ALL patients (n.50)		
Median age		12 (4-16)
Gender	Male, (N (%))	28 (56.0%)
	Female, (N (%))	22 (44.0%)
WBCs at diagnosis, median (range) $\times 10^9$/L		20.0 (11-80)
Hemoglobin at diagnosis, median (range) g/dl		9.2 (5.9-11.0)
Platelets count at diagnosis, mean ± SD $\times 10^9$ /L		39.7 ± 8.63
Bone marrow blast (%), median (range)		80.0 (35-92)
Peripheral blood blast (%), median (range)		10.0 (1-30)
Lymphadenopathy	Present, (N (%))	19 (48.7%)
Organomegaly	Present, (N (%))	11 (28.2%)
CNS infiltration	Present, (N (%))	8 (20.5%)
Induction remission response	Remission, (N (%))	40 (80.0%)
	No remission, (N (%))	10 (20.0%)
NRF2 At diagnosis	Median (Min-Max)	7.7 (6.8-10.2)
NRF2 At day 28	Median (Min-Max)	4.4 (3.2-9.1)
BCL2 At diagnosis	Median (Min-Max)	5.7 (5.1-7.8)
BCL2 At day 28	Median (Min-Max)	5.1 (4.3-8.8)

CNS (Cntral nervous system); NRF2 (nuclear factor erythroid 2- related factor 2); BCL2 (The B cell lymphoma 2).

NRF2 and BCL2 expression levels

On day 0, the expression levels of NRF2 were significantly higher than those measured on day 28 and in the control group (P<0.001) (Figure 1). Likewise, the expression of BCL2 on day 0 was considerably elevated compared to the levels observed on day 28 and in the control group (P<0.001) (Figure 2).

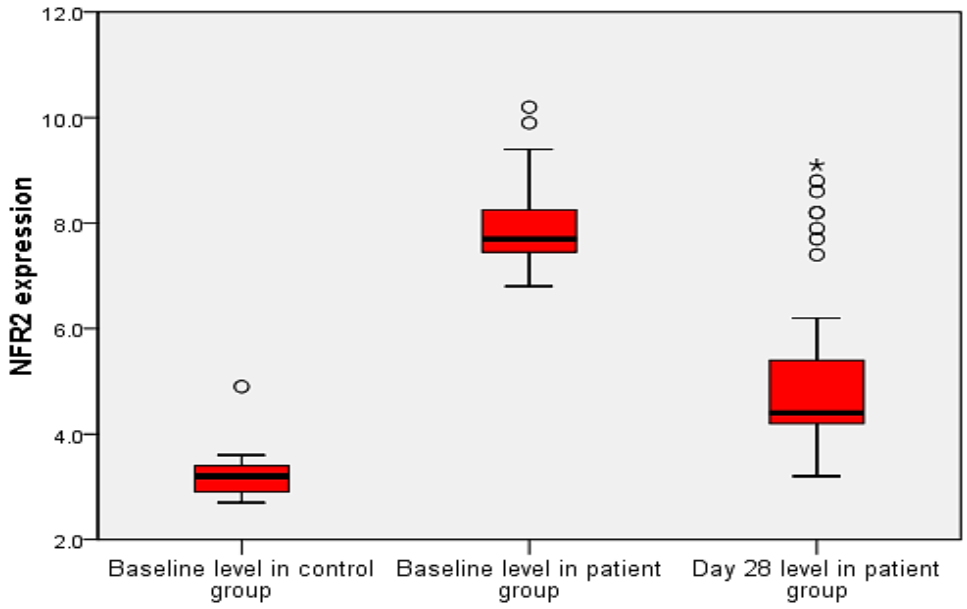

Figure 1. Illustrates the expression levels of NRF2 at the time of T-ALL diagnosis, revealing a median value of 7.7 (range 6.8-10.2). In contrast, on day 28, the median dropped to 4.4 (range 3.2 - 9.1), while the control group exhibited a median of 3.2 (range 2.7- 4.9). The differences observed were statistically significant, with P<0.001 for both comparisons. Additionally, there was a significant decrease in NRF2 expression levels from the initial measurement to day 28 (P<0.001).

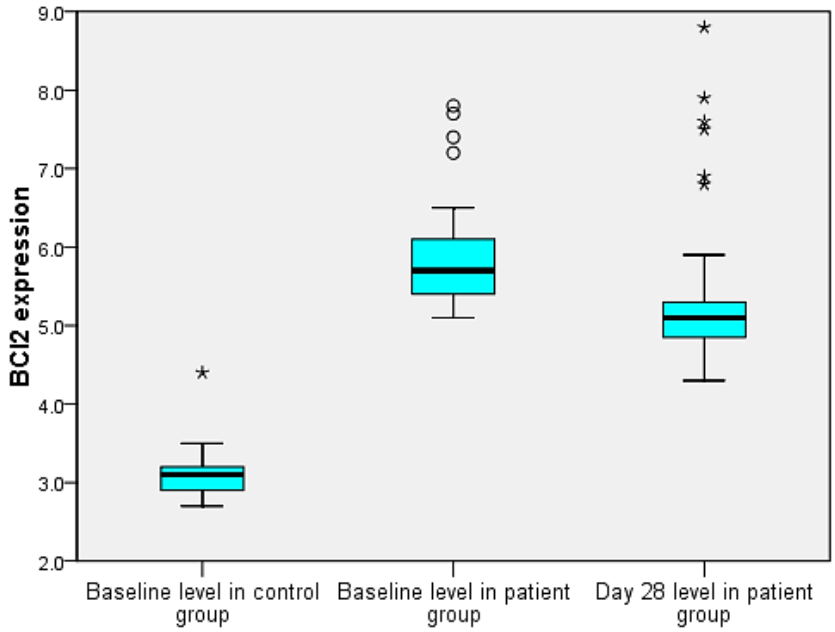

Figure 2. illustrates the expression levels of BCL2 at the time of T-ALL diagnosis, revealing a median value of 5.7 (range 5.1-7.8) In contrast, on day 28, the median dropped to 5.1 (range 4.3-8.8), while the control group exhibited a median of 3.2 (range 2.7- 4.9). The differences observed were statistically significant, with P<0.001 for both comparisons. Additionally, there was a significant decrease in BCL2 expression levels from the initial measurement to day 28 (P<0.01).

Association studies between NRF2 expression and other studied parameters

A notable positive correlation exists between NRF2 and both BCL2 and BM blast at diagnosis. Additionally, NRF2 and BCL2 exhibit a negative correlation with platelet count. No other significant correlations were identified. Furthermore, a significant positive correlation was observed between BCL2 and both peripheral blood and bone marrow blast cells (Table 2).

Table 2. Comparison of NRF2 expression at the baseline of T-ALL versus day 28 in relation to patients' characteristics.

Parameter		Baseline NRF2 Median (Min-Max)	Baseline NRF2 **At day 28**	**P[1]**	**P2**
Gender	Male	7.9 (6.9-9.9)	4.5 (3.2-8.6)	0.124	0.547
	Female	7.5 (6.8-10.2)	4.4 (3.3-9.1)		
Age (years)	1- <5	8.2 (7.2-8.4)	4.2 (4.2-9.1)	0.852	0.469
	5-10	7.7 (6.8-9.4)	4.4 (3.2-8.8)		
	>10-17	7.7 (6.9-10.2)	4.6 (3.6-8.2)		
Lymphadenopathy	No	7.5 (6.9-8.2)	4.4 (3.6-8.8)	0.010	0.569
	Yes	8.3 (6.8-10.2)	4.4 (3.2-9.1)		
Organomegaly	No	7.6 (6.9-8.8)	4.4 (3.2-8.8)	<0.001	0.006
	Yes	8.9 (6.8-10.2)	7.7 (3.3-9.1)		
CNS infiltration	No	7.6 (6.8-8.8)	4.4 (3.2-9.1)	<0.001	0.008
	Yes	9.1 (8.2-10.2)	7.8 (4.2-8.6)		
Induction remission	No	9.1 (7.5-10.2)	8.2 (7.4-9.1)	<0.001	<0.001
	Yes	7.7 (6.8-9.0)	4.4 (3.2-6.2)		
Blast count	<80.0%	7.5 (6.8-8.8)	4.3 (3.3-5.2)	0.001	0.002
	≥80.0%	8.3 (6.9-10.2)	6.8 (3.2-9.1)		
Baseline BCL2	<5.7	7.5 (6.8-7.9)	4.4 (3.3-5.2)	<0.001	0.269
	≥5.7	8.2 (7.1-10.2)	4.4 (3.2-9.1)		
Platelet count ($\times 10^9$/L)	<39.7	8.2 (6.9-10.2)	4.4 (3.2-9.1)	0.029	0.922
	≥39.7	7.6 (6.8-9.4)	4.5 (3.3-8.8)		

Mann-Whitney test, Kruskal-Wallis test. **P[1]** between groups as regard baseline NRF2, **P[2]** between groups as regard day 28 NRF2.

Predictive cutoff value of NRF2 expression levels for induction remission response

ROC analysis was conducted to identify the optimal baseline levels of NRF2 and BCL2 for predicting the response to induction remission. The results revealed that the best cut-off value for NRF2 at diagnosis was 8.3, accompanied by an area under the curve (AUC) of 0.901 (P=0.001), as illustrated in table 3.

Table 3. Performance metrics of baseline NRF2 and BCL2 in predicting remission.

	NRF2	**BCL2**
AUC	0.901	0.964
P	0.001	<0.001
95% CI	0.754-1.00	0.906-1.00
Cut off	8.3	6.1
Sensitivity (%)	93.5%	96.8%
Specificity (%)	87.5%	87.5%

Studies investigating the correlation between the expression levels of NRF2 and BCL2

A substantial positive correlation was identified at the time of T-ALL diagnosis, with a correlation coefficient of r: 0.75. Furthermore, a positive relationship was found between NRF2 expression and the number of bone marrow blast cells (r: 0.59). In contrast, NRF2 expression demonstrated a negative correlation with platelet count (r: -0.324). It is important to note that NRF2 expression did not show any significant correlation with white blood cell count or hemoglobin levels (Table 4).

Table 4. Relationship between baseline NRF2 and BCL2 alongside other parameters in the cases examined.

		NRF2
BCL2	r	0.751**
	P	<0.001
Age (years)	r	0.112
	P	0.497
WBCs ($\times 10^9$/L)	r	0.171
	P	0.298
Hb g/dl	r	0.238
	P	0.144
Platelets count ($\times 10^9$/L)	r	-0.324*
	P	0.044
PB blast (%)	r	0.053
	P	0.749
BM blast (%)	R	0.590**
	P	<0.001

The percentage of induction remission response among TALL patients with NFR2 expression ≥8.3 equaled 38.5 %, while percent of responders among patients with NFR2 <8.3 was 94.6 % (Table 5).

Table 5. Predictive value of cutoff level for NRF2 for induction remission response

Parameter		NRF2<8.3	**NRF2≥8.3**	**P**
Induction remission	yes	35(94.6%)	5 (38.5%)	<0.001
	No	2 (5.4%)	8 (61.5%)	

Regression analysis

Binary logistic regression analysis is performed to identify factors linked to remission, utilizing age, gender, clinical, and laboratory parameters.

In the univariate analysis, lymphadenopathy, organomegaly, CNS infiltration, increased white blood cell counts, elevated bone marrow blasts, and heightened baseline levels of NRF2 and BCL2 emerge as independent predictors of non-remission. However, in the multivariate analysis, only elevated NRF2 remains an independent predictor of non-remission (Table 6).

Table 6. Logistic regression for prediction of factors associated with remission:

Independent predictors	**Univariable**			**Multivariable**		
	P	**OR**	**95 % CI**	**P value**	**OR**	**95 % CI**
Age (year)	0.420	1.099	0.874-1.382			
Gender	0.697	0.729	0.148-3.596			
Lymphadenopathy	0.033	11.083	1.208-21.68	0.346	9.102	0.001-11.760
Organomegaly	0.001	7.250	4.535-19.326	0.322	9.922	0.106-12.690
CNS infiltration	0.001	13.500	5.077-27.718	0.950	8.765	0.341-12.524
WBC ($\times 10^9$/L)	0.025	1.113	1.014-1.222	0.375	1.138	0.855-1.515
Hemoglobin (g/dl)	0.313	0.934	0.630-4.239			
Platelets count ($\times 10^9$/L)	0.098	0.922	0.838-1.015			
BM blasts (%)	0.010	1.371	1.078-1.745	0.194	1.385	0.847-2.264
Blood blasts (%)	0.029	1.108	1.011-1.214	0.784	1.061	0.7023-1.277
Baseline NRF2	0.003	17.166	2.587-31.901	0.041	11.857	1.019-23.252
Baseline BCL2	0.022	22.598	2.235-53.497	0.094	11.040	0.458-39.526

OR: odds ratio, CI: Confidence interval

DISCUSSION

A major obstacle in treating T-ALL is the lack of dependable prognostic indicators aside from minimal residual disease [22]. Consequently, to enhance the clinical evaluation of this patient group, particularly those who exhibit resistance to treatments and are at an elevated risk of relapse, it is crucial to discover biomarkers that hold prognostic value. The discovery of these markers will enable a more precise stratification of patients, ultimately improving the management outcomes for those affected by T-ALL [7,23].

In recent years, numerous studies have explored the significant role of the NRF2 protein, which is crucial in cancer biology and the tumor's response to chemotherapy. Chemoresistance remains a major challenge in cancer treatment. Among the factors previously examined in T-ALL and solid tumors, NRF2 has been highlighted [24]. The overexpression of NRF2 can result in genetic instability, primarily associated with the activation of NF-kB [25].

In our research, we investigated the expression levels of NRF2 concerning the induction of remission response. The expression of NRF2 was observed to be significantly higher on day 0 in comparison to day 28, and it was also markedly elevated in patients with T-ALL relative to healthy controls. This finding is consistent with results from a previous study[26], which linked this upregulation to an increase in NFE2L2 transcription, thereby facilitating the activation of NRF2 signaling in T-ALL [7]. The heightened NRF2 expression may lead to gene instability and independent drug resistance in AML, primarily through the activation of NF-kB [22]. Furthermore, **Zheng *et al.*** [26] concluded that elevated NRF2 expression in MSCs enhances the invasion and migration of leukemia cells, thus accelerating their infiltration into extramedullary organs affected by leukemia. As a result, targeting NRF2 or inhibiting its downstream signaling molecules could represent effective therapeutic approaches for treating B-ALL patients.

Additionally, **Lee *et al*.** [13] noted that the overexpression of NRF2 reduces the efficacy of adjuvant chemotherapy in distal cholangiocarcinoma.

The findings in the present study indicated a correlation between NRF2 expression and the count of blast cells. This observation is consistent with the research conducted by **Liu *et al.*[27]**, who explored the connection between NRF2 expression and tumor mutation burden in acute myeloid leukemia (AML). Moreover, patients with NRF2 overexpression exhibited a higher frequency of gene mutations and resistance to drugs. In vitro experiments demonstrated that NRF2 overexpression provided protection to AML cells from apoptosis triggered by cytarabine, while in vivo, it increased the likelihood of drug resistance associated with gene mutations. Furthermore, NRF2 expression was closely linked to the advancement of AML and was significantly elevated in patients possessing unfavorable prognostic gene mutations. Simultaneously, a notable negative correlation was identified between NRF2 expression and the DNA mismatch repair gene replication factor C4 (RFC4) in acute myeloid leukemia (AML), as documented by **Hu *et al.*** [28].

In the current research, we assessed the correlation between NRF2 expression in T-ALL and the efficacy of chemotherapy. Patients within the T-ALL subgroup exhibiting elevated NRF2 expression showed a diminished response to induction chemotherapy. This phenomenon may be linked to the resistance of blast cells to apoptosis, as indicated by the heightened expression of BCL2 alongside increased NRF2 levels. Recent research has revealed that the combinatorial expression of BCL2 family members in AML-LSCs serves as a critical factor in determining treatment response, with MAC scoring effectively predicting patient outcomes following 5-azacytidine/venetoclax treatment [29]. Furthermore, **Yu *et al.*** [30] demonstrated that the inhibition of NRF2 could potentiate the cell death of AML induced by venetoclax through the ferroptosis pathway.

In the current study, the results of multivariate analysis indicated that elevated levels of NRF2 serve as an independent predictor for the absence of remission. This observation can be elucidated by the fact that the overexpression of NRF2 conferred protection to T-ALL blast cells against apoptosis triggered by cytarabine in vitro, at the same time, it increases the likelihood of drug resistance associated with gene mutations occurring in vivo [31]. Additionally, the increased expression of NRF2 was found to suppress the expression of MutS Homolog 2 (MSH2) protein, leading to deficiencies in DNA mismatch repair (MMR). Mechanistically, the inhibition of MSH2 by NRF2 occurred in a manner that was independent of reactive oxygen species (ROS). Furthermore, studies have shown that the increased activation of JNK/c-Jun signaling pathways in cells exhibiting NRF2 overexpression led to a decrease in MSH2 protein expression [27].

CONCLUSION

Elevated NRF2 expression at the time of T-ALL diagnosis may serve as an indicator of a suboptimal response to induction chemotherapy, primarily due to the upregulation of BCL2 expression.

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