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# Molecular analysis of *STAT3* and their association in non-Hodgkin lymphoma incidence

**Basma M. Al-Sarraj, Maha Fakhry Altaee**

**Abstract:**

**BACKGROUND:** Signal transducer and activator of transcription 3 (*STAT3*) is an essential transcription factor that functions through the Janus kinase/STAT signaling pathway, regulating cell proliferation, survival, tumorigenesis, immune surveillance, and inflammatory responses. Although dysregulated *STAT3* activity has been implicated in numerous cancers, its specific contribution to non-Hodgkin lymphoma (NHL) remains insufficiently defined.

**OBJECTIVES:** We evaluated *STAT3* gene expression and two polymorphisms (rs72823022 T/C and rs744166 A/G) to determined their association with NHL susceptibility in an Iraqi population.

**MATERIALS AND METHODS:** This research follows a case–control study design. Hematological parameters, in addition to serum urea and creatinine levels, were assessed in lymphoma patients ($n = 50$) and healthy controls ($n = 50$). STAT3 mRNA expression was quantified by reverse transcription quantitative polymerase chain reaction (RT-qPCR), and STAT3 polymorphisms were genotyped using polymerase chain reaction (PCR) followed by Sanger sequencing (ABI 3730XL platform).

**RESULTS:** *STAT3* expression was upregulated in NHL patients compared to controls (mean fold change = 7.88). Some SNP genotypes showed potential protective effects, whereas others showed a trend toward increased susceptibility; however, these associations were not statistically significant.

**CONCLUSION:** *STAT3* expression and its genetic variants may serve as potential biomarkers for the risk assessment and early detection of NHL, providing insights that could guide prognostic evaluation and therapeutic strategies.

**Keywords:**

Gene expression, non-Hodgkin lymphoma, SNPs, signal transducer and activator of transcription 3 gene

## Introduction

Cancer is a pathological condition involving uncontrolled proliferation of abnormal cells, which can invade nearby tissues and spread to distant areas of the body through the circulatory or lymphatic systems. This process, called metastasis, often leads to the formation of secondary tumors. Globally, cancer accounts for an estimated 10 million deaths annually.[1]

Lymphomas are a type of hematologic malignancy that originates from lymphocytes. Although these malignancies are genetically and histologically diverse, they share common features.[2] Nearly half of all newly diagnosed blood cancers are lymphomas, making them the sixth-most frequently diagnosed cancer type in men and women worldwide.[2] Histologically, lymphomas are generally categorized into two broad types based on the presence or absence of Reed–Sternberg cells: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[3]

*Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq*

**Address for correspondence:**
Basma M. Al-Sarraj, Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq.
E-mail: basma.hasan1206@sc.uobaghdad.edu.iq

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NHL includes most malignant lymphoid neoplasms, including tumors that arise from the lymphatic system, excluding HL, which is characterized by Reed–Sternberg.[4] NHL includes various B-cell lymphomas, such as chronic lymphocytic leukemia, follicular lymphoma, small lymphocytic lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma (DLBCL), as well as T-cell lymphomas, including Mycosis Fungoides, adult T-cell leukemia/lymphoma, and anaplastic large cell lymphoma, each with distinct clinical features and treatment responses.[4] These malignancies arise from the clonal expansion of B cells, T cells, or natural killer cells and may involve both nodal and extranodal sites.[5]

Signal transducer and activator of transcription 3 (*STAT3*) is a fundamental transcription factor that mediates several cellular processes, including cell proliferation, survival, differentiation, and immune regulation. *STAT3*, a member of the STAT family, is associated with the pathogenesis of many NHL subtypes.[6] The *STAT3* gene, located on chromosome 17q21.2, encodes a protein of 770 amino acids across 24 exons and is involved in vital physiological functions, such as angiogenesis, cancer immunosuppression, proliferation, and survival.[7] Dysregulation of *STAT3* contributes to NHL progression by promoting uncontrolled cell growth, inhibiting apoptosis, enhancing tumor survival, and creating an immunosuppressive tumor microenvironment. Persistent *STAT3* activation is also linked to resistance to chemotherapy and targeted therapies, as it upregulates the survival and drug-resistance pathways. Many studies have highlighted the prognostic significance of *STAT3* gene polymorphisms in NHL.[8]

The current study aimed to investigate the role of *STAT3* gene expression and polymorphisms in relation to an increased incidence of NHL, and to explore the potential of *STAT3* as a diagnostic and therapeutic monitoring biomarker in patients with NHL. While the role of *STAT3* in NHL has been examined in other populations, no previous studies have investigated its expression and genetic variants in the Iraqi population. Therefore, this study addresses this knowledge gap and provides important insight into the genetic and molecular factors underlying NHL in this region.

## Materials and Methods

### Study group

This research follows a case–control study and included 100 participants, comprising 50 patients diagnosed with NHL (25 male and 25 female; age range 17–80) and 50 apparently healthy controls (18 male and 32 female; age range 18–70). NHL patients were recruited from the Hematology and Bone Marrow Transplant Center (HTC), Baghdad, Iraq, and the diagnoses were confirmed by clinical, histopathological, and diagnostic evaluations. The control subjects were healthy individuals with no history of lymphoma, chronic illnesses, hormonal disorders, alcohol consumption, or smoking. Patients with other malignancies, chronic infections, autoimmune disorders, or conditions affecting study outcomes were excluded from the study. This study was approved by the Ethics Committee of the College of Science, Baghdad University, and written informed consent was obtained from all participants.

Blood samples (7 ml) were collected in three tubes: ethylenediaminetetraacetic acid for omplete blood count and genotyping, TRIzol™ tube for reverse transcription quantitative polymerase chain reaction (RT-qPCR), and a gel tube for kidney function tests (urea and creatinine).

### Determination of clinical markers

Kidney function markers, urea and creatinine, were measured to assess the overall health status of the participants and ensure normal renal function before further analyses. Measurements were performed using an enzymatic colorimetric assay, in which the target analytes react with specific enzymes to produce a color change proportional to their concentration. Absorbance was read on a Boditech autoanalyzer (Seoul, Korea) according to the manufacturer's instructions. Although these renal indices are nonspecific and may be influenced by various clinical conditions, their inclusion adhered to clinical recommendations during sample collection. This study aimed to explore the potential associations between renal function and NHL**.**

### Signal transducer and activator of transcription 3 gene expression

Total RNA was extracted from blood samples collected in TRIzol™ tubes following the manufacturer's protocol. RNA quality and concentration were assessed with a Quantus Fluorometer, and 1 µg was reverse-transcribed into complementary DNA (cDNA) using the GoTaq® 2-step RT-qPCR System. *STAT3* and *β-globin* primers were designed through Primer3 (annealing 60°C–65°C, 20–22 nt) [Table 1]. qRT-PCR was performed in 10 µL reactions on a MIC qPCR Cycler, using standard cycling conditions (95°C 1 cycle; 40 cycles of 95°C 20 s, 60°C–65°C 20 s, 72°C 20 s) with subsequent melting curve analysis (65°C–90°C). Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method, normalized to *β-globin*.[9]

### DNA extraction and SNP genotyping

Genomic DNA was isolated from peripheral blood using the ReliaPrep™ Blood gDNA Miniprep System (Promega, USA), according to the manufacturer's protocol. DNA concentration and quality were measured using a Quantus Fluorometer (Promega, USA). To amplify

a 906 bp region of the *STAT3* gene containing SNPs rs744166 and rs72823022, conventional polymerase chain reaction (PCR) was performed.

Primers were optimized at annealing temperatures of 55°C, 58°C, 60°C, 63°C, and 65°C to determine the optimal annealing temperature [Table 2].

### Polymerase chain reaction

The PCR reaction mixture (25 μL) contained 12.5 μL of GoTaq Green Master Mix, 7.5 μL of nuclease-free water, 1 μL of each primer (10 μM), and 3 μL of DNA template (20–29 ng). Thermal cycling was as follows: initial denaturation at 95°C for 5 min; 30 cycles of 95°C for 30 s, annealing at 60°C for 30 s, and 72°C for 30 s, and a final extension at 72°C for 7 min.[10,11] PCR products were verified by agarose gel electrophoresis.

### Polymerase chain reaction product sequencing

Purified PCR products were subjected to Sanger sequencing, and sequences were aligned with reference *STAT3* sequences from the NCBI GenBank to identify SNPs. Sequence data were analyzed using Geneious software to confirm the presence and genotype of the polymorphisms.

### Statistical analysis

Data analysis was conducted using the statistical packages SPSS-26 (IBM Corp.,Armonk,NY,USA) and WinPepi. The data were presented using basic statistical metrics, such as frequency, percentage, median (minimum–maximum values), mean, and standard deviation. For qualitative variables (fold-change in gene expression), data for normality were tested using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Comparisons between two groups were performed using the Independent *t*-test for normally distributed variables or the Mann–Whitney *U*-test for nonnormally distributed variables. Categorical variables were analyzed using the Chi-square test. Statistical significance was set at $P \leq 0.05$. Deviations from Hardy–Weinberg equilibrium for all genetic variations were assessed using *P* values, and WinPepi was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for genotypes and allele frequencies.

### Ethical approval

This study was conducted in accordance with the Declaration of Ethical Criteria. Before the sample was collected, verbal and analytical consent was obtained. A local ethics commission examined and authorized the study protocol, subject data, and consent form on April 18, 2024, under the registration number CSEC/0424/0033.

## Results

### Clinical characteristics

Analysis of the demographic variables revealed significant differences between patients with NHL and healthy controls. Age was significantly higher in NHL patients compared with controls (50.50 ± 17.96 vs. 39.10 ± 14.16 years; $P = 0.0006$), representing the most pronounced demographic difference. Sex distribution did not differ significantly (male: 50% vs. 32%; $P = 0.157$), indicating a balanced sex representation between the groups. A positive family history of hematological malignancy was observed in 8% of patients with NHL, whereas none of the controls had a family history ($P = 0.041$), suggesting a potential hereditary contribution. Lifestyle factors, including smoking and alcohol consumption, were low and not significantly different between groups ($P > 0.05$).

### Hematological and biochemical parameters

Hematological analysis revealed pronounced abnormalities among NHL patients. Lymphocyte counts (LYMs) were significantly elevated in patients compared with controls (8.90 ± 2.16 vs. 2.44 ± 0.65 × $10^3$/μL; $P = 0.004$), reflecting abnormal lymphocyte proliferation characteristic of NHL. In contrast, red blood cell (RBC) counts and hemoglobin (Hb) levels

**Table 1: Primers used for relative quantification of Signal transducer and activator of transcription 3 and β-globin gene expression by reverse transcription-quantitative polymerase chain reaction**

| Primer name | Sequence 5'–3' | Annealing temperature (°C) |
|---|---|---|
| β-Globin-Forward | ACACAACTGTGTTCACTAGC | 65 |
| β-Globin-Reverse | CAACTTCATCCACGTTCACC | |
| *STAT3_exp*-Forward | CTTTGAGACCGAGGTGTATCACC | 60 |
| *STAT3_exp*-Reverse | GGTCAGCATGTTGTACCACAGG | |

STAT3: Signal transducer and activator of transcription 3

**Table 2: Sequences of primers used in this study**

| Primer name | Sequence 5'–3' | Annealing temperature (°C) | Product size (bp) |
|---|---|---|---|
| *STAT3*-Forward | TGTAAAACGACGGCCAGTCCTAAGAACAGAGCAGTCATC | 55 | 906 |
| *STAT3*-Reverse | CAGGAAACAGCTATGACCTTAGCCCAGAACTAGCAAATA | | |

STAT3: Signal transducer and activator of transcription 3

were markedly reduced in patients (RBC: 3.57 ± 0.78 vs. 4.38 ± 0.55 × $10^6$/μL; Hb: 10.24 ± 2.06 vs. 12.99 ± 1.17 g/dL; both $P < 0.0001$), indicating significant anemia. Platelet (PLT) counts were also significantly lower among patients (193.4 ± 117.5 vs. 272.5 ± 74.71 × $10^3$/μL; $P = 0.0001$), whereas total WBC counts showed no significant difference ($P = 0.757$).

Biochemical markers further distinguished NHL patients from controls. Both erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH) were markedly elevated in patients (ESR: 71.28 ± 19.61 vs. 10.96 ± 5.36 mm/hr; LDH: 295.5 ± 99.82 vs. 153.5 ± 35.38 U/L; both $P < 0.0001$), reflecting systemic inflammation and increased cellular turnover. Urea levels were moderately higher (35.72 ± 3.28 vs. 26.83 ± 8.14 mg/dL; $P = 0.013$), whereas creatinine showed no significant difference (0.76 ± 0.38 vs. 0.69 ± 0.28 mg/dL; $P > 0.05$). Overall, the most notable differences in NHL patients included older age, positive family history, elevated ESR and LDH levels, increased LYMs, and reduced RBC and Hb levels, highlighting substantial demographic, hematological, and biochemical disturbances associated with NHL pathogenesis.

## Signal transducer and activator of transcription 3 gene expression

Following RNA extraction, cDNA was synthesized through reverse transcription. Annealing and melting temperatures were optimized at 60°C and 65°C, respectively, to ensure efficient amplification of the *STAT3* target gene. Relative gene expression was quantified by RT-qPCR [Figure 1] and normalized to a housekeeping gene using the $2^{-\Delta\Delta Ct}$ method. *STAT3* expression was 7.88-fold higher in NHL patients compared with controls [Figure 2], demonstrating substantial upregulation.

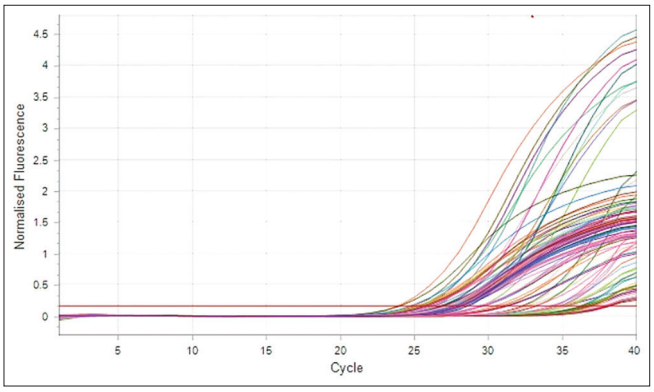


**Figure 1:** Plots of amplification of gene of Signal transducer and activator of transcription 3 via reverse transcription quantitative polymerase chain reactiontranscription 3 via reverse transcription quantitative polymerase chain reaction

## Signal transducer and activator of transcription 3 gene polymorphisms

Two SNPs with polymorphic frequencies *rs72823022* (T/C) and *rs744166* (A/G) were identified within the 906 bp PCR-amplified region of the *STAT3* gene [Figure 3 and Table 3].

Sequencing analysis of rs72823022 [Figure 3a] revealed three genotypes in NHL patients: TT (43%), TC (7%), and CC (0%), corresponding to T and C allele frequencies of 93% and 7%, respectively. Statistical analysis revealed no significant variation in the heterozygous TC group (OR = 1.19; 95% CI = 0.31–4.67; $P = 1.000$). Similarly, the mutant C allele exhibited an OR of 1.18 (95% CI = 0.33–4.42; $P = 1.000$), indicating no statistically significant association. Nevertheless, the presence of the TC genotype and mutant C allele may represent a potential risk factor for increased disease susceptibility in patients with NHL.

Sequencing of rs744166 [Figure 3b, Table 3] identified three genotypes in patients with NHL: AA (11%), AG (25%), and GG (14%), with A and G allele frequencies of 47% and 53%, respectively. Statistical analysis showed no significant variation for the GG genotype (OR = 0.64; 95% CI = 0.19–2.12; $P = 0.428$), AG genotype (OR = 1.47; 95% CI = 0.46–4.71; $P = 0.317$), or for the mutant G allele (OR = 0.72; 95% CI = 0.40–1.31; $P = 0.317$). These findings suggest that the GG genotype and the mutant G allele may act as protective factors, potentially decreasing the risk of NHL.

## Signal transducer and activator of transcription 3 haplotype and linkage disequilibrium

In humans, there are two possible haplotypes for every segment of DNA, but there may be many

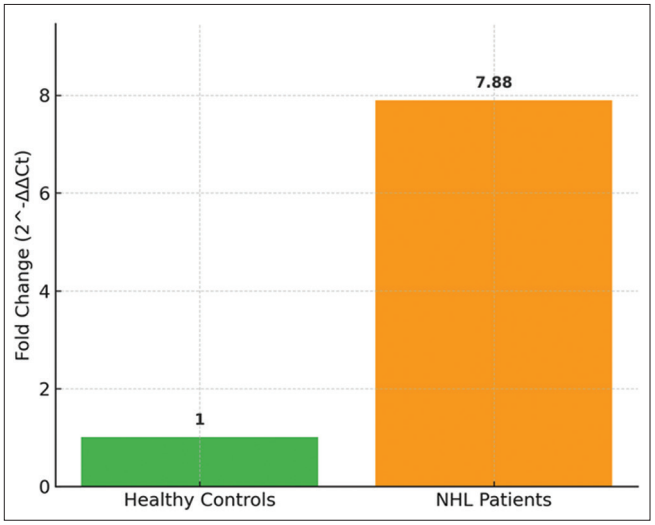


**Figure 2:** Signal transducer and activator of transcription 3 gene expression fold change ($2^{-\Delta\Delta Ct}$) in non-Hodgkin lymphoma patients compared with healthy controls. NHL: Non-Hodgkin lymphoma

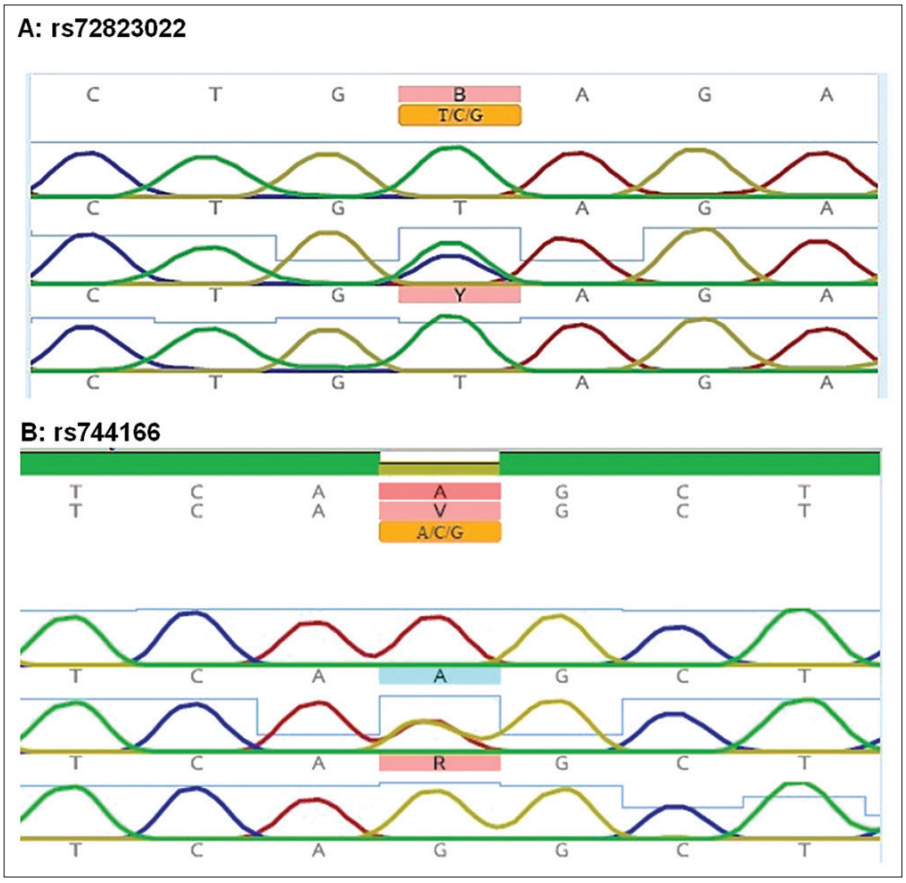


**Figure 3:** DNA sequence chromatogram of two Signal transducer and activator of transcription 3 gene SNPs (rs72823022, [T/C/G] and rs744166 [A/C/G]). Showing the heterozygous genotype of each SNP in non-Hodgkin lymphoma patients. The reference sequences of SNPs are denoted with A and B

**Table 3: Genotype and allele frequency of single-nucleotide polymorphism of signal transducer and activator of transcription 3 gene and their Hardy–Weinberg Equilibrium in patients and controls**

| STAT3 gene SNPs Genotype and allele frequency | Patients (*n*=50), *n* (%) | Control (*n*=50) | *P*; OR (95%CI) |
|---|---|---|---|
| *rs72823022* genotype frequency | | | |
| TT | 43 (86) | 44 (88) | Reference |
| TC | 7 (14) | 6 (12) | 1.000 (NS) |
| | | | 1.19 (0.31–4.67) |
| CC | 0 | 0 | - |
| HWE *P* value | 0.594 (NS) | 0.651 (NS) | - |
| *rs72823022* allele frequency | | | |
| T | 93 (93) | 94 (94) | Reference |
| C | 7 (7) | 6 (6) | 1.000 (NS) |
| | | | 1.18 (0.33–4.42) |
| *rs744166* genotype frequency | | | |
| AA | 11 (22) | 11 (22) | Reference |
| AG | 25 (50) | 17 (34) | 0.597 (NS) |
| | | | 1.47 (0.46–4.71) |
| GG | 14 (28) | 22 (44) | 0.428 (NS) |
| | | | 0.64 (0.19–2.12) |
| HWE *P* value | 0.979 (NS) | 0.043* | - |
| *rs744166* allele frequency | | | |
| A | 47 (47) | 39 (39) | Reference |
| G | 53 (53) | 61 (61) | 0.317 (NS) |
| | | | 0.72 (0.40–1.31) |

*$P<0.05$. *P*=Probability value, *n*=Frequency, NS=Not significant, SNPs=Single nucleotide polymorphism, HWE=Hardy–Weinberg Equilibrium, STAT3=Signal transducer and activator of transcription 3, OR=Odds ratio, CI=Confidence interval

more haplotypes in the population as a whole. Each haplotype is a combination of alleles for different polymorphisms that occur on the same chromosome.[12] There were no significant links between specific *STAT3* gene haplotypes and NHL [Table 4]. These findings suggest that *STAT3* haplotypes may not influence NHL etiology. Linkage disequilibrium (LD), the nonrandom association of alleles from different loci, can provide valuable information on the structure of haplotypes in the human genome and is often the basis for evaluating the association of genomic variation with human traits among unrelated subjects.[13] Delta (D), relative delta (D′), and *P* value were employed as metrics to assess the magnitude of the link. D′ is a numerical value ranging from 0 to 1, where a value of 1 indicates the highest linkage level. To assess the LD between various pairs of *STAT3* and haplotypes, the computation involved the determination of D, accompanied by the Pearson correlation coefficient ($r^2$). This approach aimed to evaluate the strength of the association.[14]

## Discussion

The pathogenesis of NHL is a multifactorial process involving genetic mutations, immune suppression, alterations in the tumor microenvironment, and environmental influences such as viral infections, particularly Epstein–Barr virus. Studies of genetic variation have provided insights into the role of individual susceptibility in NHL development. Therefore, the possible association between *STAT3* gene polymorphisms and NHL susceptibility in an Iraqi population was investigated for the first time in the present study. Fifty NHL patients from Iraq and 50 age-, sex-, and ethnicity-matched controls were analyzed for the presence of *STAT3* expression and SNPs (*rs72823022*, *rs744166*).

**Table 4: Estimated numbers and frequencies of haplotypes (*rs744166* and *rs72823022*) of the Signal transducer and activator of transcription 3 in non-Hodgkin lymphoma patients and controls**

| Haplotype *rs744166* and *rs72823022* | Patients | | Controls | | OR | 95% CI | *P* |
|---|---|---|---|---|---|---|---|
| | *n* | Frequency | *n* | Frequency | | | |
| C - A | 1.17 | 0.012 | 3.43 | 0.034 | 0.334 | 0.040–2.769 | 0.286 (NS) |
| C - G | 5.83 | 0.058 | 2.57 | 0.026 | 2.437 | 0.526–10.465 | 0.250 (NS) |
| T - A | 45.83 | 0.458 | 35.57 | 0.356 | 1.532 | 0.869–2.784 | 0.139 (NS) |
| T - G | 47.17 | 0.472 | 58.43 | 0.584 | 0.635 | 0.363–1.111 | 0.110 (NS) |

*Significant ($P \leq 0.05$). All frequencies <0.03 were ignored in the analysis. NS=Nonsignificant, CI=Confidence interval, OR=Odds ratio

**Table 5: Demographic characteristics and chemical tests of non-Hodgkin lymphoma patients and healthy controls**

| Characteristics | Groups | | *P* |
|---|---|---|---|
| | Patients with NHL (*n*=50), *n* (%) | Control (*n*=50), *n* (%) | |
| Age (years), mean±SD | 50.50±17.96 | 39.10±14.16 | 0.0006*** |
| Sex | | | |
| Male | 25 (50) | 18 (36) | 0.157 (NS) |
| Female | 25 (50) | 32 (64) | |
| Family history | | | |
| Yes | 4 (8) | 0 | 0.041* |
| No | 46 (92) | 50 (100) | |
| Smoking | | | |
| Yes | 3 (6) | 0 | 0.078 (NS) |
| No | 47 (97) | 50 (100) | |
| Alcohol | | | |
| Yes | 1 (2) | 0 | 0.314 (NS) |
| No | 49 (98) | 50 (100) | |
| WBC ($10^3$/μL), mean±SD | 7.437±1.434 | 7.890±1.911 | 0.757 (NS) |
| LYM ($10^3$/μL), mean±SD | 8.897±2.155 | 2.437±0.6548 | 0.004** |
| RBC ($10^6$/μL), mean±SD | 3.573±0.777 | 4.375±0.553 | <0.0001**** |
| HB (g/dL), mean±SD | 10.24±2.059 | 12.99±1.174 | <0.0001**** |
| PLT ($10^3$/μL), mean±SD | 193.4±117.5 | 272.5±74.71 | 0.0001*** |
| Urea (mg/dL), mean±SD | 35.72±3.282 | 26.83±8.141 | 0.013* |
| ESR (mm/h), mean±SD | 71.28±19.61 | 10.96±5.363 | <0.0001**** |
| LDH (U/L), mean±SD | 295.5±99.82 | 153.5±35.38 | <0.0001**** |
| Creatinine mg/dL, mean±SD | 0.760±0.379 | 0.686±0.283 | 0.272 (NS) |

*$P$<0.05, **$P$<0.01, ***$P$<0.001. P=Probability value, NS=Nonsignificant, LDH=Lactate dehydrogenase, ESR=Erythrocyte sedimentation rate, PLT=Platelet, HB=Hemoglobin, RBC=Red blood cell, LYM=Lymphocyte count, WBC=White blood cell count, NHL=Non-Hodgkin lymphoma, SD=Standard deviation

This study is the first to investigate the demographic and clinical markers and possible genetic features for the prognostication and diagnosis of diseases. The results in Table 5, clearly showed that significant ($P < 0.05$) for most demographic and chemical test, These findings are consistent with previous studies in which family history has been consistently identified as a significant risk factor for NHL.[15] Another study found that family history was not significantly associated with increased NHL.[16] The findings of the present study align with previous epidemiological evidence, indicating no significant association between smoking and the overall risk of NHL. However, some studies have reported a possible subtype-specific relationship, particularly with an increased risk of follicular lymphoma among smokers.[17] These discrepancies may be attributed to variations in study design, population genetics, or exposure classification. In contrast, alcohol intake has consistently demonstrated an inverse association with NHL risk in several observational studies, suggesting its potential protective role.[18] The underlying mechanisms remain unclear but may involve modulation of immune function or anti-inflammatory effects associated with moderate alcohol consumption. Further research is needed to clarify these associations and to determine whether lifestyle factors influence specific biological pathways in NHL pathogenesis. High ESR levels are associated with other markers, such as LDH, and our results are consistent with studies where it was found that high ESR and LDH levels describe high aggressiveness and poor treatment response of the diseases.[19] LDH is an important indicator of the severity of NHL; LDH > 400 is associated with a greater increase in WBC, a greater decrease in Hb, the presence of B-symptoms, the presence of mediastinal mass, and advanced disease.[20] Ultimately, renal function, including urea and creatinine levels in patients, and elevated levels of urea and creatinine in NHL patients occurring as a result of direct tumor impact or treatment, were studied, and significant variation was seen with urea. Our results are consistent with previous studies.[21] Other studies have found that advanced NHL and Burkitt's lymphoma cause elevated levels of urea and creatinine due to tumor lysis syndrome or treatment.[22]

*STAT3* upregulation is a hallmark of many cancers and hematological malignancies and plays a role in NHL.[23] The current study is consistent with a previous study, which showed that upregulation of *STAT3* occurs in aggressive subtypes of NHL, such as DLBCL and ALCL.[24] However, *STAT3* levels increased in patients with genetic mutations or postchemotherapy, but differed from one another, which found no significant variation.[25] Another study examined *STAT3* expression levels in patients with DLBCL compared to the control group, and it was found to be decreased.[26] These variations in *STAT3* gene levels can only be explained by racial and demographic variations.

According to gene polymorphism studies, *STAT3* plays a complex role in autoimmune diseases and carcinogenesis, notably in hematological malignancies, and stimulates oncogenesis. *STAT3* SNPs have been identified as major risk factors for NHL, aiding the understanding of its genetic basis and treatment options.[8] The current investigation of an Iraqi community found that *STAT3* SNPs (*rs744166* A > G, *rs72823022* T > C) reflect different effects on NHL risk. *rs744166* A > G was associated with a lower NHL risk, especially the GG genotype and the G allele. These results disagreed with those of previous studies, where the *STAT3* polymorphism *rs744166*, the GG genotype compared with AG, was significantly associated with a decrease in lymphoma.[27] In contrast, there are no studies related to *rs72823022* in NHL risk and other diseases, and in our results, this SNP was shown to be associated with a lower incidence of NHL. In addition, LD analysis [Figure 4] of *STAT3* gene SNPs showed a weak correlation, indicating independent inheritance. D′ and $r^2$ values were low for these SNPs, independently affecting *STAT3* gene characteristics. Although this study did not establish a direct statistical correlation between *STAT3* expression and the analyzed SNPs, exploring this relationship could provide further insight into how genetic variation modulates transcriptional activity. Variants such as *rs72823022* and *rs744166* may influence transcription factor binding, RNA splicing, or mRNA stability, ultimately affecting *STAT3* expression and the downstream signaling pathways involved in NHL pathogenesis. Future studies with larger sample sizes and functional assays, including allele-specific expression or reporter gene analyses, are warranted to clarify the mechanistic role of *STAT3* polymorphisms in gene regulation and disease susceptibility. These findings highlight the interplay of demographic factors, clinical markers, gene expression, and genetic variation

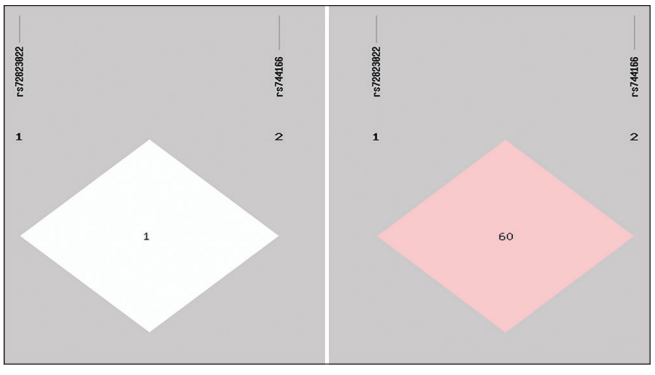


**Figure 4:** Linkage disequilibrium (LD) analysis among SNPs of Signal transducer and activator of transcription 3 (*STAT3*) gene in non-Hodgkin lymphoma (NHL) patients. *STAT3*- SNPs (*rs744166* and *rs72823022*) in NHL patients and controls. $r^2$: Correlation coefficient among each pair of SNPS (0-1); ': Scaled D value (D value represents LD for each pair of SNPS) with an interval between (−1, 1)

in NHL. The identification of unique *STAT3* SNPs as potential risk modulators enhances our understanding of the genetic basis of NHL and provides a foundation for future diagnostic, prognostic, and therapeutic strategies in the Iraqi population.

## Conclusion

This study demonstrated that *STAT3* plays a multifaceted role in NHL pathogenesis through both gene expression and genetic variation. Upregulation of *STAT3* and the presence of specific SNPs, particularly *rs72823022* and *rs744166*, differentially influenced NHL susceptibility in the Iraqi population, highlighting the complex interplay between genetic factors and disease development. These findings improve our understanding of the genetic determinants underlying NHL, and underscore the potential of *STAT3* as a biomarker for risk assessment, prognosis, and personalized therapeutic strategies. Further studies with larger cohorts and functional analyses are warranted to clarify the mechanistic pathways linking *STAT3* signaling to lymphoma progression.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Sriharikrishnaa S, Suresh PS, Prasada KS. An introduction to fundamentals of cancer biology. In: Optical Polarimetric Modalities for Biomedical Research. Cham: Springer International Publishing; 2023. p. 307-30.
2. Fardin MF, Akter M. Review of blood cancer and its types. J Mol Pharm Regul Aff 2021;3:18-26.
3. Polepole P, Mudenda VC, Munsaka SM, Zhang L. Spectrum of common Hodgkin lymphoma and non-Hodgkin lymphomas subtypes in Zambia: A 3-year records review. J Health Popul Nutr 2021;40:37.
4. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of non-Hodgkin's lymphoma. Med Sci (Basel) 2021;9:5.
5. Costa RO, Pereira J, Lage LA, Baiocchi OC. Extranodal NK-/T-cell lymphoma, nasal type: What advances have been made in the last decade? Front Oncol 2023;13:1-17.
6. Samad MA, Ahmad I, Hasan A, Alhashmi MH, Ayub A, Al-Abbasi FA, *et al*. STAT3 signaling pathways in health and disease. MedComm 2025;6:e70152.
7. Liu Y, Liao S, Bennett S, Tang H, Song D, Wood D, *et al*. STAT3 and its targeting inhibitors in osteosarcoma. Cell Prolif 2021;54:e12974.
8. Chen Y, Lan Q, Zheng T, Zhao N, Holford TR, Lerro C, *et al*. Polymorphisms in JAK/STAT signaling pathway genes and risk of non-Hodgkin lymphoma. Leuk Res 2013;37:1120-4.
9. Samawi FT, Al-Dujaily SS, Al-Saidi MK, Abdulfattah SY, Saeed ZZ. Expression of Protamine-1 gene and association with Interleukin-12 gene in infertile men: A case-control study in Iraqi patients. Iraqi J Sci 2023;64:2798-808.
10. Ammar KA, Altaee MF. Recurrent TMPRSS2 genetic polymorphism and its role in prostate cancer in Iraqi patients. Iraqi J Agric Sci 2022;53:272-7.
11. Abdullah D, Aloubaidy RM. Genetic polymorphisms of caspases 8 and 9 in Iraq. Iraqi J Agric Sci 2022;53:505-14.
12. Fesenko DO, Ivanovsky ID, Ivanov PL, Zemskova EY, Agapitova AS, Polyakov SA, *et al*. A biochip for genotyping polymorphisms associated with eye, hair, skin color, AB0 blood group, sex, Y chromosome core haplogroup, and its application to study the Slavic population. Mol Biol (Mosk) 2022;56:860-80.
13. Huang L, Rosen JD, Sun Q, Chen J, Wheeler MM, Zhou Y, *et al*. TOP-LD: A tool to explore linkage disequilibrium with TOPMed whole-genome sequence data. Am J Hum Genet 2022;109:1175-81.
14. Lu S, Zhong H, Liu F, Zhou K, Tang W, Yang B, *et al*. STAT4 gene polymorphism may be associated with microscopic polyangiitis susceptibility in a Chinese Guangxi population: A case-control analysis based on propensity score matching. Hum Immunol 2025;86:111241.
15. Ebrahimi P, Ghezel MA, Hosseini-Berneti SH, Lashkarbolouki AH, Karami M, Nikbakht HA. Mortality trend of hematological neoplasms in Babol, Northern Iran (2013-2021). Arch Iran Med 2024;27:654-9.
16. Shadid AM, Alsaber N, Shadid AM, Mubarak FR, Makkawi M, Algahtani FH, *et al*. Assessing the relationship between blood transfusion products and non-Hodgkin's lymphoma incidence: A longitudinal retrospective cohort study (2004-2022). J Family Med Prim Care 2025;14:1069-72.
17. Msallem E, Pacquement H, Olivier L, Brugières L, Landman Parker J, Garnier N, *et al*. Association between perinatal factors and childhood lymphoma-a pooled analysis of the ESCALE and ESTELLE studies (SFCE). Pediatr Blood Cancer 2025;72:e31439.
18. Psaltopoulou T, Sergentanis TN, Ntanasis-Stathopoulos I, Tzanninis IG, Tsilimigras DI, Dimopoulos MA. Alcohol consumption and risk of hematological malignancies: A meta-analysis of prospective studies. Int J Cancer 2018;143:486-95.
19. Otasevic V, Mihaljevic B, Milic N, Stanisavljevic D, Vukovic V, Tomic K, *et al*. Immune activation and inflammatory biomarkers as predictors of venous thromboembolism in lymphoma patients. Thromb J 2022;20:20.
20. de Pádua Covas Lage LA, De Vita RN, de Oliveira Alves LB, Jacomassi MD, Culler HF, Reichert CO, *et al*. Predictors of survival, treatment modalities, and clinical outcomes of diffuse large B-Cell lymphoma in patients older than 70 years are still unmet medical needs in 2024, based on real-world evidence. Cancers 2024;16:1459.
21. Cao K, Wu JC, Hernandez M, Ganti L. Steroid-induced tumor Lysis syndrome accompanied by diabetic ketoacidosis and acute renal failure in a non-Hodgkin lymphoma patient. Cureus 2022;14:e24491.
22. Simões SR, Santos IG, Matos IP, Campos CC, Malheiros DN, Leite RP, *et al*. Primary extranodal T/NK-cell lymphoma,nasal subtype,primary of the testis:A case report. Hematol Transfus

Cell Ther 2024;46 Suppl 4:S290-1.
23. Zhang HF, Lai R. STAT3 in cancer-friend or foe? Cancers 2014;6:1408-40.
24. Zhou Z, Zhu P, Ge J, Li Q, Li H, Zhe N, *et al*. Gene regulatory mechanisms of T cell exhaustion in diffuse large B cell lymphoma based on single-cell transcriptome data. Leuk Res 2024;146:107588.
25. Fasan A, Kern W, Grossmann V, Haferlach C, Haferlach T, Schnittger S. STAT3 mutations are highly specific for large granular lymphocytic leukemia. Leukemia 2013;27:1598-600.
26. Kwon HJ, Yang JM, Lee JO, Lee JS, Paik JH. Clinicopathologic implication of PD-L1 and phosphorylated STAT3 expression in diffuse large B cell lymphoma. J Transl Med 2018;16:320.
27. Gu C, Can C, Liu J, Wei Y, Yang X, Guo X, *et al*. Genetic polymorphisms in immune-related genes contribute to the susceptibility to and survival from lymphoma. Cancer Med 2023;12:14960-78.