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The cytokine milieu orchestrates the Th1/Th2/Th17 and Treg cells roles in acute lymphoblastic leukemia patients

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Abstract

Background and objective: T cells perform a crucial role in mediating immune responses to a diversity of pathogens. Different types of T cells play a great role in immune response, including T helper cells 1 (Th1), T helper cells 2 (Th2), T helper cells 17 (Th17), and T regulatory cells (Treg cells). Each of these cells produces different types of cytokines, and irregularities of their levels have been linked to various malignancies.

Methods: In this case-control study, demographic information was collected from patients suffering from acute lymphoblastic leukemia (ALL), and then concentrations of C-reactive protein (CRP) and total white blood cell (WBC) count, beside interleukins 2,4,10,13,17 and 22(IL-2, IL-4 IL-10, IL-13, IL17, IL22), tumor necrosis factor alpha (TNF-α) and interferon gamma (INF-γ) cytokines were tested in their sera.

Results: Th-associated pro-inflammatory cytokines IFN-γ, IL-2, TNF-α, IL-4, IL-13, IL-17, and IL-22 were significantly decreased in ALL patients compared to healthy controls. On the other hand, immunosuppressive cytokine IL-10 associated with Treg cells was markedly elevated in the patient group. Elevated CRP and WBC levels were also observed in ALL patients, indicating systemic inflammation.

Conclusion: The cytokine profile in ALL patients is indicative of a shift to immunosuppressive status that could facilitate leukemic development. The reduction in pro-inflammatory cytokines and elevation of IL-10 levels point towards suppressed anti-tumor immunity. These findings highlight the significance of Th1/Th2/Th17/Treg cell interactions in ALL and suggest that manipulation of cytokine disbalance could yield new diagnostic or therapeutic avenues.

Keywords: Interleukins, Lymphoblastic leukemia, TNFα, T helper cells, T regulatory cells.

Introduction

Leukemia is a dangerous and potentially fatal disease that originates in the blood and red bone marrow (1). Leukemia is a monoclonal cancer that starts with one cell, so malignancy arises from

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a stem cell in bone marrow (2). This disease is mainly found in young children, but you can also see it in adults. There are two types of it. B-cell lineage has molecular bases, and T-lymphoid lineage has no molecular bases. Each of them has its own abnormality and therapeutic implications (3). Acute lymphoblastic leukemia (ALL) is a chromosomal mutation type translocation, and body cell mutation leads to leukemia. It has been proven that the application of treatment in the pediatric type to young adults shows great improvement to young adult patients. Treatment for relapsed ALL patients does not give effective treatment no matter how old the patient is. The appearance of the disease in the next generation enables a better understanding of the disease's genetic inheritance in ALL patients (4, 5). Two types of white blood cells have a significant role in cell-mediated immune response (adaptive immunity): helper T cells, sometimes named by the antigen that is present on their surface (CD4), and cytotoxic T cells, or cluster of differentiation 8 (CD8) (6). In children, a type of T cell produces interleukin 2; in children, these cytokines can regulate the function of other immune cells (7). Some interleukins are used as markers to identify the response to treatment in ALL patients; for example, the increase of IL-6 causes a decrease of IFN-gamma in the children with ALL (8).

There is proof that immune cytokines are linked with the conclusion in pediatric leukemia. IL-10 (interleukin-10) and TNF-α, as well as TGF-β (transforming growth factor β) and IFN-γ, are expected to have opposite effects in anti-leukemia immunity. T-ALL can be diagnosed when there are few productions of Th1 cytokines TNF-α and IFN-γ. As far as IFN-γ increase, peripheral blast decrease. This happened because in leukemic patients the host helper T1 is repressed. TNF-α is regarded to be one of the important pro-inflammatory procurators, with an optional ability to induce apoptosis. Production of low TNF-α increases tumor formation and vice versa by increasing apoptosis in cancer cells (9).

Materials and methods

Patients

The current study was authorized by the Ethics Committee of the college of pharmacy, Hawler Medical University. (No: Sc. E.C. 10H2) Beside that, all patients were provided a written informed consent to sign for their participation in this study. This study was conducted in Nanakali Hospital for Cancer and Blood Diseases in Erbil City. A questionnaire form was filled out for each participant to record their demographic information. Peripheral blood samples were collected and serum was kept in -20 to examine IFN gamma, IL2, IL4, IL10, IL13, IL17A, IL22, TNF alpha levels by using Human Th1/ Th2/ Th17/ Treg Multiplex ELISA Kit (Arigo Biolaboratories Corp., Taiwan)

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Multiplex enzyme immunoassay is a sandwich immunoassay conducted semi-quantitatively to measure various cytokines of Th1, Th2, Th17, and Treg cells (e.g., IFN-γ, IL-2, IL-4, IL-10, IL-13, IL-17A, IL-22, TNF-α). Microtiter wells are pre-coated with anti-cytokine-specific antibodies. Standards and samples are added, and cytokines bind to their specific antibodies. After washing, detection antibodies are added, followed by an HRP-conjugate (Horseradish Peroxidase) that binds to the detection antibodies. TMB (3,3',5,5'-Tetramethylbenzidine) substrate is added, resulting in a color change in proportion to cytokine concentration. The reaction is stopped, and absorbance is read at 450 nm.

Statistical analysis: The Chi-Square Test of Independence (x^2) was used to find out the association between two nominal categorical variables, while the independent samples T-test was used to compare the mean between variables. IBM SPSS Statistics is used to analyze the data.

Results

Table1 represents the demographic parameters of the study, most of the participants were aged more than 30 years old (50%) followed by 11-20 (32.14%), 21-30 (10.71%), and 1-10 years old (7.14%) respectively. Most of them were single (57.14%), living in urban (53.57), unemployed (60.07%), and obese (BMI 30.36%).

Table 2 shows that there is a significant difference between patients and control groups with each of the marital status and level of education variables independently using the chi-square test because their P-values (0.000 and 0.031) are less than the significant level of $\alpha = 0.05$. For example, most of the participants who have leukemia cancer are single (69.6%) compared to married (30.4%). Most of the participants who have leukemia cancer are educated (67.4%) compared to illiterate (32.6%). In addition, there is no statistically significant difference between the patient and control groups with each of the residence, economic status, and occupation variables because their P-values (0.213, 0.082, and 0.063) are higher than the significant level of $\alpha = 0.05$.

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Table 1. Descriptive statistics for demographic questions

		N	%
Age	1-10	4	7.14
	11-20	18	32.14
	21-30	6	10.71
	31+	28	50.00
BMI	Underweight	7	12.50
	Normal weight	16	28.57
	Overweight	16	28.57
	Obesity	17	30.36
Age diagnosis	1-10	5	10.87
	11-20	19	41.30
	21-30	5	10.87
	31+	17	36.96
Marital Status	Single	32	57.14
	Married	24	42.86
Residence	Urban	30	53.57
	Rural	26	46.43
Economic Status	Low	25	44.64
	Medium	31	55.36
Occupation	Governmental employee	19	33.93
	Unemployed	37	66.07
Education	Illiterate	15	26.79
	Primary	13	23.21
	Intermediate	10	17.86
	High school	10	17.86
	Diploma	2	3.57
	Bachelor degree	6	10.71

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Table 2. Association between patient and control groups with demographic questions

			Group		Total	chi-square	P-value	Result
			Patient	Control				
Marital Status	Single	N	32	0	32	16.232	0.000**	highly
		%	69.6	0.0	57.1			significant
	Married	N	14	10	24			
		%	30.4	100.0	42.9			
Residence	Urban	N	23	7	30	1.321	0.213	Non-
		%	50.0	70.0	53.6			significant
	Rural	N	23	3	26			
		%	50.0	30.0	46.4			
Economic	Low	N	23	2	25	2.991	0.082	Non-
Status		%	50.0	20.0	44.6			significant
	Medium	N	23	8	31			
		%	50.0	80.0	55.4			
Occupation	Governmental employee	N	13	6	19	3.691	0.063	Non-
		%	28.3	60.0	33.9			significant
	Unemployed	N	33	4	37			
		%	71.7	40.0	66.1			
Education	Illiterate	N	15	0	15	4.454	0.031*	Significant
		%	32.6	0.0	26.8			
	Educator	N	31	10	41			
		%	67.4	100.0	73.2			
Total		N	46	10	56			
		%	100	100	100			

**It is significant at the 0.01 level

*It is significant at the 0.05 level

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Moreover, table 3 demonstrates that most of the participants were nonsmokers (95.7%) and no significant difference were found between patient and control regarding the chronic disease status P-values (0.192 and 0.119) respectively.

Table 4 shows significant difference between the patient and control groups regarding their C- reactive protein level (CRP) and their total white blood cell count (WBC); P-values (0.001 and 0.014).

Table 3. Association between patient and control groups with smoker, chronic disease, and type of chronic disease

			Group			chi-square	P-value	Result
			Patient	Control	Total			
Smoking	Yes	N	2	6	8	20.777	0.000	highly significant
		%	4.3	60.0	14.3			
	No	N	44	4	48			
		%	95.7	40.0	85.7			
Chronic disease	Yes	N	6	3	9	1.753	0.192	Non-significant
		%	13.0	30.0	16.1			
	No	N	40	7	47			
		%	87.0	70.0	83.9			
Type of chronic disease	Hypertension	N	2	3	5	3.600	0.119	Non-significant
		%	33.3	100.0	55.6			
	Both	N	4	0	4			
		%	66.7	0.0	44.4			
Total		N	6	3	9			
		%	100	100	100			

**It is significant at the 0.01 level

*It is significant at the 0.05 level

Table 4. CRP and WBC mean differences between patient and control groups

		N	Mean	Std. Deviation	t-test	P-value	Result
CRP	Patient	46	48.898	89.831	3.513	0.001	highly significant
	Control	10	2.338	1.464			
WBC	Patient	46	5.460	4.659	2.634	0.014	Significant
	Control	10	8.270	2.492			

**It is significant at the 0.01 level

*It is significant at the 0.05 level

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IL-2, IFN-γ, and TNF-α levels were significantly lower in acute lymphoblastic leukaemia (ALL) patients compared to healthy subjects. IL-2 levels (Figure 1A) were drastically reduced in ALL patients (~50 pg/mL) compared to healthy individuals (>110 pg/mL), and the difference was statistically significant ($P < 0.01$). Similarly, the levels of IFN-γ (Figure 1B) decreased drastically from ~55 pg/mL in healthy individuals to below 10 pg/mL in ALL patients ($P < 0.001$). TNF-α levels (Figure 1C) also decreased dramatically, from ~6.5 pg/mL in controls to ~1 pg/mL in ALL patients ($P < 0.01$). These persistent decreases in key pro-inflammatory cytokines reveal impaired or inhibited immune function in ALL patients.

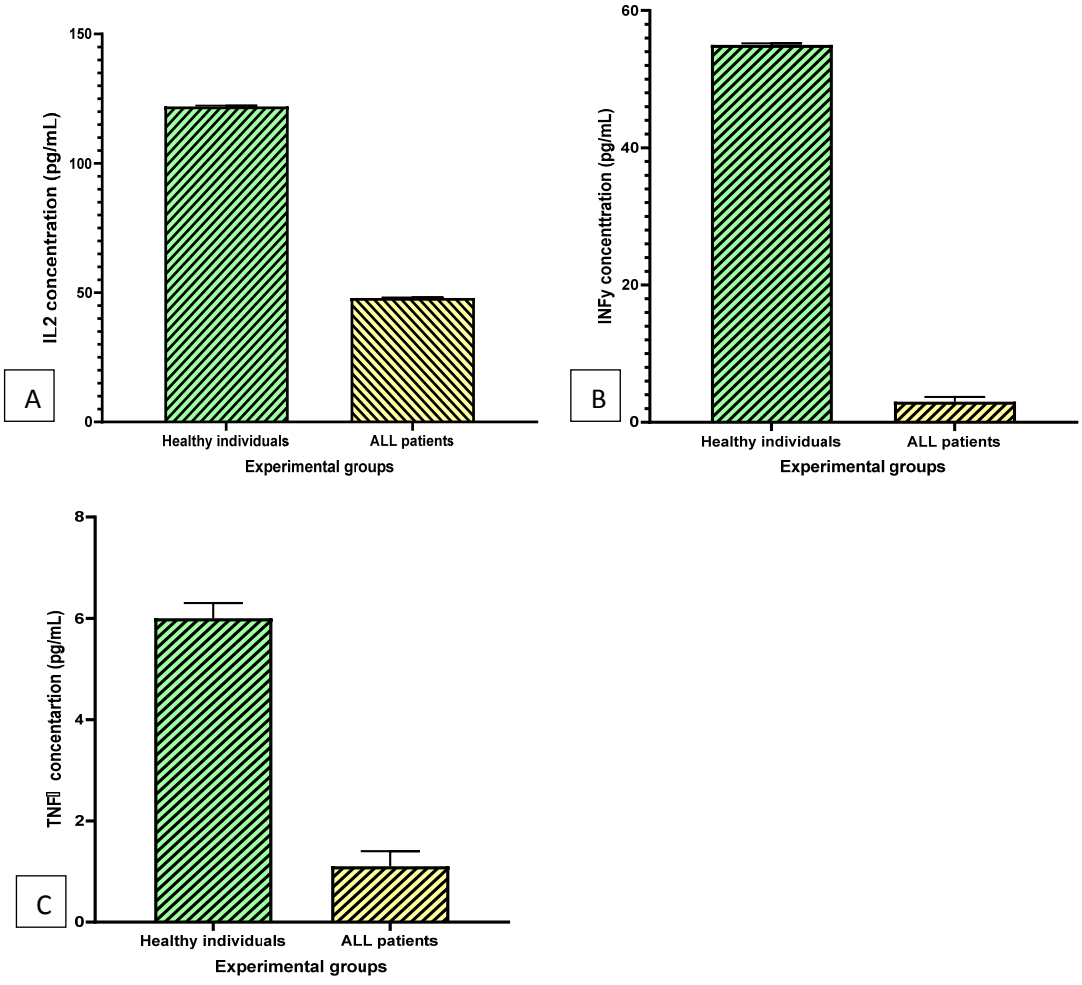

Figure 1. Cytokine Expression Profiles in Healthy Individuals and ALL Patients

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Th2 type cytokines IL-4 and IL-13 were also considerably lower in ALL patients. Levels of IL-13 (Figure 2A) fell from ~2.1 pg/mL in controls to ~1.0 pg/mL in ALL patients ($P < 0.05$), while IL-4 (Figure 2B) levels fell dramatically from ~2.1 pg/mL to less than 0.5 pg/mL ($P < 0.01$). These findings point to a wide-ranging immunosuppressive profile in ALL, undermining both Th1 and Th2 immune pathways.

Statistical analysis revealed that there was a significant decrease in Th17-associated cytokines in all patients when compared with healthy controls. As demonstrated in panel A, the average serum level of IL-22 in healthy subjects was 6.0 ± 1.0 pg/mL, whereas that of ALL patients was considerably lower at 2.0 ± 2.0 pg/mL ($P < 0.01$). Similarly, in (panel B), the mean level of IL-17 in normal controls was 1.4 ± 0.05 pg/mL compared to 0.2 ± 0.1 pg/mL in ALL patients, and the difference was highly significant ($P < 0.001$). These highly different values reflect a strong down regulation of Th17 cell response in the ALL group, (Figure 3).

The level of IL-10, a key anti-inflammatory cytokine that is linked to regulatory T (Treg) cells, was notably higher in ALL patients than in healthy controls. The average level of IL-10 in ALL patients was around 17–18 pg/mL, whereas it was around 3 pg/mL in the healthy control group. Statistical analysis revealed that the difference was extremely significant ($P < 0.001$). This marked increase in IL-10 represents an augmented immunosuppressive environment in ALL, which is likely to be mediated by enhanced Treg function, and which may contribute to impaired anti-tumor immunity in these patients, (Figure 4).

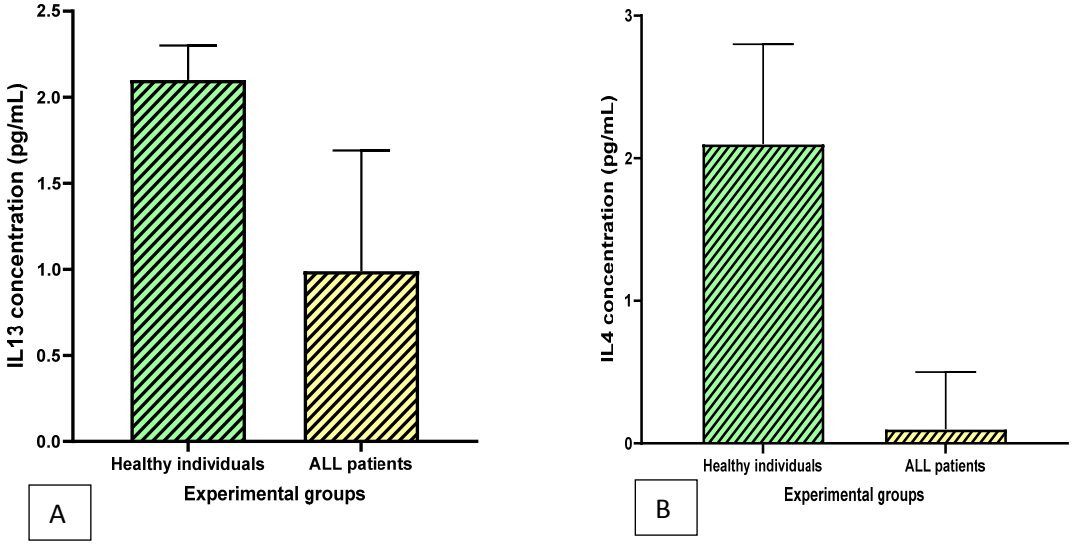

Figure 2. Profiles of cytokine expression in healthy subjects and ALL patients

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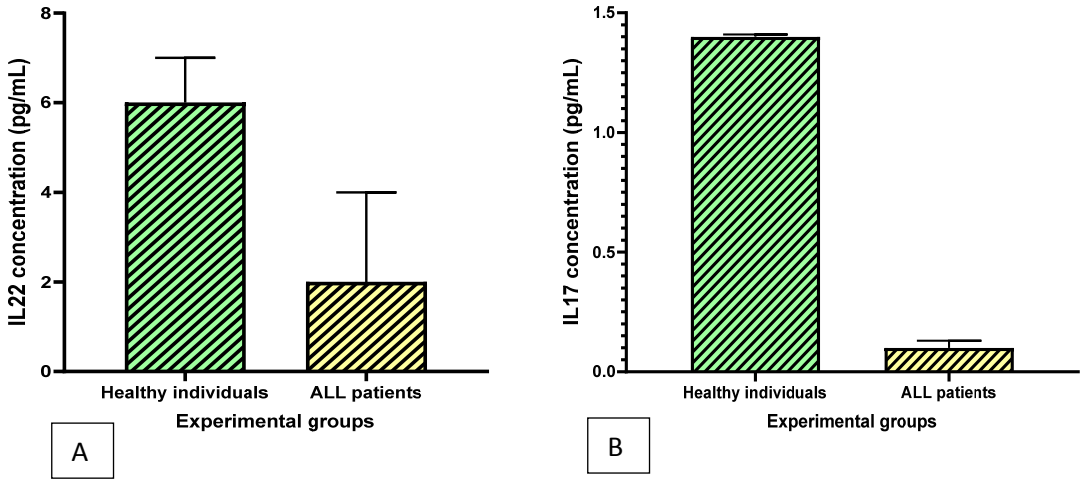

Figure 3. Th17 Cell-Associated Cytokines (IL-17 and IL-22)

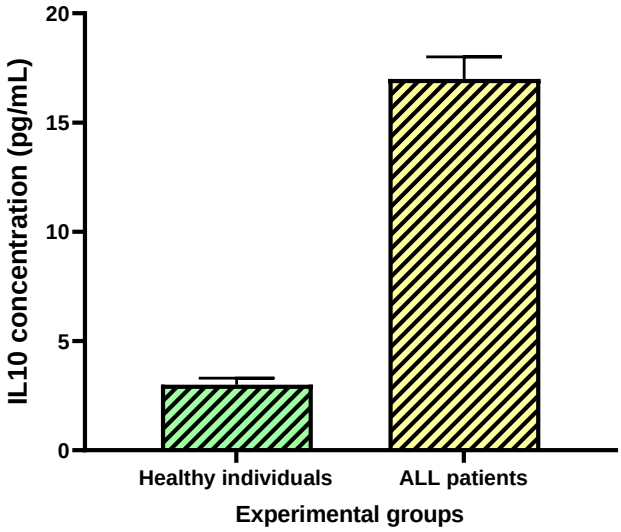

Figure 4. Treg Cell-Associated Cytokine (IL-10)

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Discussion

The statistics reveal that 50% of the population is 31+ years old. This is followed by 32.14% who are 11–20 years old. Just 7.14% are in the 1–10 age bracket. It indicates that the population is skewed toward the older adult population (3). Research like (10) demonstrates that chronic diseases such as type 2 diabetes and hypertension are more common in older populations, and this aligns with the population skew. The most prevalent BMI classification is obesity (30.36%), followed by overweight (28.57%) and then normal weight (28.57%), with only 12.5% being underweight. The high prevalence of overweight and obesity indicates worldwide patterns in rising BMI. According to the World Health Organization (11), the worldwide obesity prevalence nearly tripled since 1975, and lifestyle determinants including physical inactivity and unhealthy diet are a significant factor. 41.30% diagnosed within ages 11–20, then 31+ (36.96%), Just 10.87% diagnosed between ages 1–10 and 21–30. The high percentage diagnosed in young adulthood or later in life could reflect delayed diagnosis of chronic conditions. This echoes research by (12) who found a greater prevalence of late diagnosis of metabolic and cardiovascular conditions among low-resource communities. 57.14% are unmarried, and 42.86% are married. This distribution of marital status can have implications for health outcomes. (13)state that single persons undergo more psychological stress and social support loss, which can influence disease management and quality of life. Urban dwellers constitute 53.57%, while 46.43% are rural. This almost equal division can have implications for access to healthcare and lifestyle. Those in urban areas are also more likely to have access to health care but lead fewer active lives that expose them to higher risks of obesity and related illness (14). Medium economic status was most prevalent (55.36%), Low economic status represented 44.64%. Economic status is a key indicator of health literacy, access to care, and dietary options. According to the Global Health Observatory (15), individuals with lower-income status are more likely to experience postponed care and worsening chronic conditions. The majority of them (66.07%) are not working, and only 33.93% are government-employed. The high unemployment rates might be associated with adverse health effects through the mechanisms of restricted access to medical care and reduced socioeconomic buffering. As researched by (16)unemployment is related to higher rates of depression and chronic illness, particularly in post-pandemic environments. Finally, the educational level differed according to table 1.

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In conclusion, demographic profile delineates a population at risk of non-communicable diseases (NCDs), particularly against the background of high obesity rates, unemployment, and urban dwelling. These trends indicate the need for focused public health campaigns, early screening, and economic stimulus.

This report takes into account correlations with control and patient groups versus major demographic factors. For the chi-square tests, examined the relationship of marital status, place of residence, economic status, occupation, and education to health group status. Statistically significant and non-significant results are interpreted within the context of the literature for the last few years. There is a statistically very significant difference (χ^2 = 16.232, P = 0.000). All the controls are married, whereas 69.6% of the patients are single. This implies that spouse support is a determinant of health status, where unmarried individuals are at increased risk of mental or chronic ailments (17). No relationship (χ^2 = 1.321, P = 0.213). The division between rural and urban residence does not vary significantly. Urban areas can have better access to medical facilities, while rural areas may lead healthier lives due to reduced pollution and increased physical activity (14) Not statistically significant (χ^2 = 2.991, P = 0.082), although there exists a trend for possible impact. Financial hardship remains an established indicator for minimizing access to health services (15). The relationship is not statistically significant (χ^2 = 3.691, P = 0.063), although on the borderline of significance. A greater percentage of controls are working. Unemployment leads to ill health via financial insecurity as well as psychosocial tension (16). There is a statistically significant relationship (χ^2 = 4.454, P = 0.031). All controls are educated but 32.6% of the patients are illiterate. Education significantly impacts health through improved literacy, communication, and well-informed health choices (18).

Finally, the results indicate that education and marital status are highly correlated with group variation, pointing to their possible contribution to health outcomes. Although other variables like occupation and economic status were not found to be statistically significant, their trend indicators need to be followed up.

The analyzes the relationship between patient/control group status and factors such as smoking habits, presence of chronic diseases, and type of chronic disease. Statistical significance was assessed using chi-square tests. A highly significant association was observed between smoking status and group (χ^2 = 20.777, P = 0.000). Only 4.3% of patients were smokers compared to 60% of controls. This finding is opposite

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to conventional reports of associations between smoking and health decline, but could indicate underreporting by patients or increased health consciousness in the patient cohort following diagnosis (19)No significant association between chronic disease presence and group status was found (χ^2 = 1.753, P = 0.192). Although it is understood that chronic diseases such as cardiovascular disease or diabetes affect health outcomes, their occurrence in this study did not differ significantly between groups (15). The nature of the chronic disease (hypertension only compared to hypertension and diabetes) was not significantly related to group status (χ^2 = 3.600, P = 0.119). Patients were more likely than controls to have both diseases. This can suggest a trend of comorbidity clustering within patients, if not statistically so in this instance (20).

In total, of the variables examined, smoking was the only one to show a statistically significant difference between patient and control populations. Chronic disease and type of chronic disease were not significant, but trends observed may be worthy of investigation in larger populations. To compare the mean differences of CRP (C-reactive protein) and WBC (white blood cell) counts in patient and control groups. CRP; The average CRP was significantly greater in patients (48.898) compared to controls (2.338), with a t-test of 3.513 and a P-value of 0.001, which is highly significant. Whereas WBC: Patients had a lower average number of WBC (5.460) compared to controls (8.270), t-test = 2.634, and P-value = 0.014, which shows that the difference is significant. In current research, CRP and WBC levels differ radically between controls and patients, and CRP is very high among patients, possibly because of an inflammatory reaction (21).

Th1 cells are essential effectors of cell-mediated immunity and are known for their production of IFN-γ, IL-2, and TNF-α. These cytokines are responsible for the activation of macrophages, maintenance of cytotoxic T cell function, and are central to the regulation of intracellular pathogens as well as tumor surveillance. The dramatic decrease in IFN-γ, TNF-α, and IL-2 levels seen in ALL patients reflects a depressed Th1 immune response. This suppression concurs with past findings suggesting that ALL leads to a compromised immune environment, which may play a role in leukemic cell immune evasion and disease progression (22). This observation is supported by recent research; IFN-γ plays a critical role in anti-leukemic immune surveillance, and its downregulation may favor leukemic cell proliferation and immune evasion (23).TNF-α has dual roles, and at physiological levels, is pro-immune activation; its decrease signals immunosuppression in ALL (24). IL-2, needed for T cell proliferation and NK

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cell function, is typically low in ALL, impairing adaptive immunity (25). Th2 cells produce cytokines like IL-4 and IL-13, which are central to controlling immune responses, including B-cell activation and antibody production.

Reduced IL-4 in ALL; the chronic reduced IL-4 level in ALL patients suggests that Th2-directed responses are suppressed. This might reflect leukemia-associated immune dysregulation where malignant transformation blocks the typical Th2 response (26). IL-4 plays a critical role in B-cell proliferation and survival; hence its suppression is capable of resulting in defective humoral immunity in ALL. IL-13 and ALL; another character Th2 cytokine with redundant actions to IL-4. Reduced IL-13 generation in ALL has been documented in research, demonstrating that suppression of IL-4 and Th2 immunity is not exclusive to IL-4 (27). Downregulation of both IL-4 and IL-13 in ALL marks a deviation from the activity of Th2, presumably facilitating immune evasion and leukemia cell proliferation. T helper 17 (Th17) cells are a subset of $CD4^+$ T cells that produce interleukin-17 (IL-17) and interleukin-22 (IL-22), which are critical for inflammation, autoimmunity, and anti-tumor immunity. The data presented show the profoundly diminished level of both IL-17 and IL-22 in ALL patients' serum when compared to normal individuals, indicating suppressed Th17 response.

This Th17 cytokine suppression in ALL is corroborated by several recent studies suggesting that Th17 cells may have a protective immunological role in hematologic malignancies. IL-17 has been shown to augment anti-leukemic immunity through the activation of neutrophils and the facilitation of cytotoxic T cell activity (28). Similarly, IL-22 is involved in tissue repair and immune surveillance, and decreased levels of it have been implicated with blunted immune reactivity in ALL patients (29). The reduced Th17-related cytokines in ALL could be a result of immunosuppression induced by tumors, where leukemic cells create a tolerogenic microenvironment that suppresses productive T cell responses. Alternatively, leukemia-induced breakdown of cytokine networks and dendritic function might skew T helper cell differentiation towards non-Th17 lineages (30). Notably, Th17 modulatory opportunity might offer a therapeutic option. Th17 cell activity strategies to augment or strategies to promote IL-17/IL-22 signaling might restore antitumor immunity in ALL, but such strategies must be scrutinized carefully because Th17 cytokines otherwise possess a dual pro-inflammatory and possibly tumorigenic effect in other contexts (31). Tregs, which are characterized by the expression of FOXP3 and IL-10 production, regulate overactive immune responses. But in cancer scenarios like

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acute lymphoblastic leukemia (ALL), their immunosuppressive function is hijacked by leukemic cells to avoid immune detection and destruction.

Unexpected rise of IL-10 level among ALL patients, reflecting enhanced activity of Treg cells. This rise is a potential reason for inhibition of cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and Th1 responses—cell types essential for anti-leukemic immunity (32). Enhanced IL-10 has also been reported to inhibit antigen presentation by dendritic cells, yet another mechanism of immune suppression. A few publications have reported higher frequencies of Tregs and IL-10 levels to be correlated with poor prognosis and increased risk of relapse among ALL patients, most notably in children (33). The leukemic niche may even actively recruit or expand Treg populations through cytokine signaling (e.g., via TGF-β and IL-2), hence sustaining immune suppression. In contrast, IL-10 has context-dependent anti-inflammatory and anti-proliferative functions, and its role in tumor biology is complex. While its suppressive functions can dampen antitumor immunity, IL-10 has been suggested to also inhibit inflammatory damage and even tumor-promoting inflammation in certain contexts (34). Such dual roles render IL-10 and Treg modulation the subject of active research towards immunotherapeutic targeting in ALL (35).

Conclusion

Acute lymphoblastic leukemia (ALL) cytokine profile demonstrates an extreme immunological imbalance characterized by diminished Th1, Th2, and Th17 responses and exaggerated Treg function. The drastic decline in IFN-γ, IL-2, and TNF-α reveals a compromised Th1-mediated cellular immune response, which is essential for ideal anti-tumor immunity. Meanwhile, the inhibition of IL-4 and IL-13 portrays impaired Th2 responses, thereby leading to imperfect humoral immunity. Similarly, reduced IL-17 and IL-22 levels signify impaired Th17-mediated inflammatory and antitumor immunity. In contrast, high IL-10 levels are indicative of enhanced Treg function that facilitates an immunosuppressive microenvironment for leukemic development and immune evasion. This immunological signature underscores the dynamic interaction between cytokines and T cell subsets in ALL pathogenesis. A complete understanding of this cytokine dysregulation not only delineates the mechanisms of immune evasion but also uncovers potential targets for immunomodulatory therapies. Modulating the Th1/Th2/Th17/Treg axis may present novel strategies for restoring effective immune responses and enhancing outcomes in patients with acute lymphoblastic leukemia (ALL).

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Competing interest

The authors declare that they have no competing interests.

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