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Some immunological parameters and interleukin level associated with Chronic myelogenous leukemia patients in Al Anbar governorate

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ABSTRACT

Context: Tumor necrosis factor (TNF)-α and other cytokines play a role in the pathophysiology of chronic myeloid leukemia (CML), however their prognostic importance in these conditions remains unclear. The authors evaluated the correlation between serum cytokine levels and clinical outcomes in individuals with CML in the present study.

Methodology: Serum concentrations of TNF-a, interleukin (IL)-1 receptor antagonist, IL-6, IL-5, IL-3, IFN 1a, C3, and C5 were assessed in patients with CML1 or CML2 seeking treatment at Al-Anbar Oncology Center. Univariate and multivariate analyses were conducted to examine relationships with clinical outcomes.

Outcomes: Elevated TNF-a levels were associated with diminished performance status, increased leukocyte counts, and heightened cytokine levels. Additionally, a robust positive association was observed between TNF-a, INF-a, IL-1a, IL-6, IL-5, IL-3, C3, and C5 in patients with chronic myeloid leukemia (CML).

Conclusions: Elevated serum levels of TNF-a, INF-a, IL-1a, IL-6, IL-5, IL-3, C3, and C5 in CML patients signify the severity of the disease.

Keywords: *cytokines, disease duration, Chronic myeloid leukemia, INF α, TNF-α.*

1. INTRODUCTION

Advanced age, adverse cytogenetic risk, and performance status are frequently utilized to forecast clinical outcomes in patients with chronic myeloid leukemia (CML).One to twelve Nonetheless, prognostic variability persists, necessitating the identification of novel prognostic variables. The initial observational observations regarding the cytoreductive effect of interferon α (IFNα) in patients with chronic myeloid leukemia (CML) originated in the 1980s, coinciding with the introduction of IFNα treatment at the M.D. Anderson Cancer Center in Houston, Texas [1]. IFNα promotes sustained significant and occasionally complete cytogenetic remissions (CCR) lasting for months, and in rare cases, years [2]. IFNα induces antileukemic responses through the activation of T-cell immunity [3] and also enhances humoral immunity against CML antigens [4]. Certain measures of innate immunity, which seemingly contribute to anticancer immunity, are also positively affected by IFNα [5]. This may clarify the effectiveness of IFNα therapy in vivo by coordinating a network of immune cells rather than activating specific populations. Additional methods by which IFNα modulates disease progression are associated with its antiproliferative action. Nonetheless, prolonged administration of IFNα may induce or aggravate immune-mediated problems [6]. IFNγ is an inflammatory cytokine essential for both innate and adaptive immunity . Demonstrated to exhibit dysregulated expression in the bone marrow of leukemia patients [7].

Tumor necrosis factor (TNF)-α is a principal effector and regulatory cytokine having a multifaceted involvement in the pathogenesis of various immune-mediated disorders and hematologic malignancies, including chronic myeloid leukemia (CML)[8].TNF-a promotes the proliferation of dividing cells, leading to hypercellularity or eliciting apoptosis in their mature progeny, resulting in pancytopenia. It is synthesized by monocytes and T cells, however it is found in all forms of leukemia.

Elevated levels of TNF-a transcripts correlate with an increased proportion of cells in the S-phase and confer resistance to induction treatment[9].

Interleukin 1 (IL-1) stimulates the proliferation of chronic myeloid leukemia (CML) blasts. The unregulated proliferation of CML cells is ascribed to the disproportionate release of IL-1 and its natural receptor antagonist[10]. IL-3 promotes the differentiation of hematopoietic stem cells into myeloid and lymphoid progenitor cells and enhances the proliferation of myeloid lineage cells (Hercus et al., 2013). The receptor IL-3R is demonstrated to be overexpressed in chronic myeloid leukemia [11]. IL-6 exerts several effects on the proliferation of CML blasts, facilitating and sustaining their growth via the IL-6/IL-6 receptor signaling pathway. Serum concentrations of IL-6 serve as a significant prognostic indicator in diffuse large cell lymphoma and chronic lymphocytic leukemia[12].

IL-5 irreversibly suppresses spontaneous CML blast proliferation and colony formation, while reducing the release of IL-1a, IL-1b, TNF-a, granulocyte-macrophage colony-stimulating factor, and IL-6, contingent upon the presence of specific exogenous growth factors[13].nTo our knowledge, the function of these cytokines has not been comprehensively investigated in CML. This study investigated the prognostic relevance of pretreatment blood concentrations of TNF-a and other cytokines in individuals with newly diagnosed chronic myeloid leukemia (CML).Typically, the patients for whom the levels of a specific cytokine were assessed were not the same individuals for whom the levels of another cytokine were evaluated[14]. Consequently, we performed distinct analyses to evaluate the predictive relevance of TNF-a, IL-6, IL-5, IL-3, IL-1, IFN 1a, C3, and C5. It was crucial to ascertain if patients underwent evaluation of their cytokine levels. To resolve this issue, we evaluated cytokine levels among three groups, two of which comprised leukemia patients defined by disease duration: severe chronic myeloid leukemia (CML1 >1 year) and moderate chronic myeloid leukemia (CML2 <1 year).

2. METHODOLOGY

This case-control study focused on patients with hematological malignancies (chronic leukemia) undergoing therapy at the Al-Anbar Oncology Center in Al-Anbar, Iraq, from March to November 2023. Experienced medical practitioners utilized patient histories, fundamental clinical characteristics, and biochemical analyses to diagnose the participants. The study comprised two groups, each consisting of 110 people. Twenty healthy individuals constituted the control group, whereas ninety leukemia patients were categorized according to the duration of their illness, comprising seventy with CML1 (Group >1 year) and twenty with CML2 (Group <1 year). Each participant had blood extraction to evaluate TNF-a, interleukin (IL)-1 receptor antagonist, IL-6, IL-5, IL-3, IFN 1a, C3, and C5. Demographic information, including age, sex, medical conditions, and duration of illness, was collected from each subject's personal and medical history. Before blood collection, each research participant provided their informed consent. Each research group had participants from whom six milliliters of anticoagulated K3-EDTA blood were extracted. Subsequently, the blood was divided into milliliter aliquots to facilitate a comprehensive blood count. Centrifugation was conducted for 10 minutes at 4°C at a speed of 1006 Xg to isolate the plasma from the residual blood. The isolated plasma was subsequently stored at -20 degrees Celsius (-20 ˚C) for the quantification of TNF-a, interleukin (IL)-1 receptor antagonist, IL-6, IL-5, IL-3, IFN 1a, C3, and C5 utilizing MyoBioSource Sandwich ELISA kits.

2.1 Statistical analysis

The statistical analysis system SPSS (V.26) was employed to assess the impact of several elements, including hematological and immunological parameters, across three groups in the current study, comprising patients and controls. This study utilized the T-test to compare means. The Pearson correlation coefficient test was conducted using the Statistical Package for the Social Sciences (SPSS).In the current investigation, the probabilities were 0.05 and 0.01.

3. RESULTS AND DISCUSSIONS

3.1 Demographic calculations

A total of ninety individuals with leukemia were enrolled in the study, consisting of 70 patients in Group CML 1 (32 females and 38 males) with a mean age of 47.09 ± 4.07 years, and 20 patients in Group CML 2 (7 females and 13 males) with a mean age of 41.90 ± 0.97 years. Furthermore, 20 patients (9 females and 11 males) with a mean age of 45.6 ± 2.7 years were recruited as the control group; demographic data are included in Table1.

Table 1. Demographic distribution of study participants

Groups	Control(n=20)	CML1(n=70)	CML2(n=20)
Sex	(F=9, M=11)	(F=32, M=38)	(F=7, M=13)
Mean age ±SD	45.6 ± 2.7	47.09 ± 4.07	41.90 ± 0.97
P Value	0.011	0.034	0.021

3.2. Hematological profiles of healthy and chronic myeloid leukemia (CML) samples.

A comprehensive blood analysis was conducted to examine the differences among the three groups in this investigation, utilizing the Mean ± standard deviation (SD). Table 2 presents the results for hemoglobin, white blood cells, lymphocytes, hematocrit, red blood cells, and platelets for both patients and the control group.

Table 2. Hematological parameter comparison between patient and control groups

Group	WBC(x 10^9 mL)	Lymphocytes(x 10^9 mL)	Hb (g/dl)	PLT(x 10^9)	HCT (%)	RBC(x 10^6 mL)
CML1	9.03±0.27	3.64 ± 0.019	10.14± 1.06	90.36 ± 6.95	22.34± 0.05	2.46± 0.38
Control	7.24 ±0.11	2.25 ± 2.52	14.51 ±0.9	272.5 ± 2.44	46.36 ±0.74	4.93 ±0.31
T- test	3.426	4.212	0.857**	41.073**	3.144**	0.514**
p-value	0.0291	0.661	0.0001	0.0001	0.0001	0.0001
CML2	8.62±0.09	2.86± 1.02	11.62 ±1.75	114.2 ± 3.6	30.44± 0.84	3.81± 0.87
Control	7.24 ±0.11	2.25 ± 2.52	14.51 ±0.9	272.5 ± 2.44	46.36 ±0.74	4.93± 0.31
T- test	2.101	2.972	0.441**	36.003**	2.017**	0.381**
p-value	0.0194	0.403	0.0001	0.0001	0.0001	0.0001
**P<0.001						

The current investigation revealed substantial variations in WBC levels between patients and healthy people, whereas other studies indicated elevated WBC levels in patients. The hemoglobin levels in this investigation were markedly different between patients and healthy controls, with anemia observed in all patient categories without substantial variations. The present study concurs with Al-abady's research[15], indicating that anemia was observed in all patients without substantial variation. The findings align with the research conducted by Aslam et al.,[16] which elucidated substantial disparities in CBC parameters, such as hemoglobin, platelets, and WBC levels, between CML1 patients and controls (P=<0.001). The findings of the present investigation indicated considerable disparities in the white blood cell counts between the patient and control groups, although the expected substantial rise in white blood cells among leukemia patients. There was a significant elevation in white blood cell count, but the secondary CML2 and relapsed groups exhibited an appropriate quantity of white blood cells, resulting in a balance that approached the normal WBC value.

3.3 Interlaken levels in the control and patient groups

The present study revealed a statistically significant disparity between patients and healthy controls regarding serum levels of TNF-a, interleukin (IL)-1 receptor antagonist, IL-6, IL-5, IL-3, IFN 1a, C3, and C5. The Mean ± SE for both groups is detailed in Table 3, with a P-value of 0.0001 for TNF-a, interleukin (IL)-1 receptor antagonist, IL-6, IL-5, IL-3, IFN 1a, C3, and C5, respectively.

Table 3. Comparison between the control and patients' group in TNF-a, interleukin (IL)-1, IL-6,IL-5, IL-3 , IFN 1a , C3 , and C5.

Group	IL-1 α	IL-5	IL-6	IL-3	INF α	TNF α	C3	C5
CML1	91.4± 3.67	115± 0.97	211 ±0.92	61.02± 0.84	190 ±14.05	582± 30.21	22.01± 0.07	101 ±12.6
Control	13.2 ± 4.74	9.72 ± 0.73	45.40 ±1.05	54.04 ± 0.81	30.54±4.01	29.95 ±7.10	2.89 ± 0.92	93.24±10.0
T- test	4.506	6.04	3.11	6.31	11.26	10.83	0.88	9.54
p-value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
CML2	156 ±4.77	197 ±3.22	160 ±2.14	30.45 ±0.67	28.9± 13.04	65.81 ±6.07	11.03 ±0.84	157 ±10.64
Control	13.2 ± 4.74	9.72 ± 0.73	45.40 ±1.05	54.04 ± 0.81	30.54±4.01	29.95 ±7.10	2.89 ± 0.92	93.24±10.0
T- test	3.74	2.75	4.33	5.08	9.07	8.9	0.36	10.08
p-value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

The current study is the first to correlate the levels of IL-6, IL-5, IL-3, IL-1α, INFα, and TNF-α in the serum of CML patients, despite several prior investigations in Iraq and neighboring countries measuring these cytokines, including the study by Boersma et al.[17]. The present study demonstrated increased levels of IL-6, IL-5, IL-3, and IL-1 α in CML patients relative to healthy controls. This finding aligns with prior research, such as the Iraqi study by Boersma et al., which indicated higher levels of IL-1 α in CML patients compared to controls[17]. A separate study indicated that serum concentrations of IL-6, IL-5, and IL-3 may serve as predictive serum markers at the diagnosis of CML[18]. The pathophysiology of numerous hematological malignancies, including chronic myeloid leukemia (CML), is associated with cytokine dysregulation, and plasma cytokine levels correlate with disease progression and survival outcomes. Our results align with the prior research by Lissoni et al.[19], which identified an elevation of IL-3 in CML patients. Cytokines are soluble molecules generated by bodily cells or as a result of tissue injury or specific diseases, including cancer[17]. CML cytokines were generated by either immune cells or blasts; however, it remains uncertain whether they contribute to the exacerbation of pathogenicity[20]. CML has been associated with alterations in cytokine levels, which are connected to autoimmune diseases, allergies, and cancer. Tumorigenesis is associated with an inflammatory milieu, and tumors are characterized as dynamic, interactive systems[21]. A study by Boersma et al. elucidated a higher significance of IL-1α in patients with chronic myeloid leukemia compared to controls[17]. A separate study indicated that serum levels of IL-5 may serve as predictive serum markers at the diagnosis of CML[22]. The pathophysiology of certain hematological malignancies, including chronic myeloid leukemia (CML), is associated with cytokine dysregulation, and plasma cytokine levels correlate with disease progression and survival outcomes. Our results align with the prior research by Lissoni et al., which identified elevated levels of IL-3 in individuals with CML[19].

Cytokines are soluble molecules generated by bodily cells or as a result of tissue injury or specific diseases, including cancer. CML cytokines were generated by either immune cells or blasts; however, it remains unclear whether they contribute to the exacerbation of pathogenicity. CML has been associated with alterations in cytokine levels, which are connected to autoimmune diseases, allergies, and cancer. Tumor development is associated with an inflammatory milieu, and tumors seem to function as dynamic, interactive systems[23]. The levels of TNF-α exhibited a notable elevation in patients relative to healthy controls, suggesting that this proinflammatory cytokine is associated with an augmented risk of CML. This outcome aligns with other research, including a study by AL-Khateeb et al.[24], which established that greater serum levels of TNF-α serve as a negative prognostic indicator for survival and Effective Free Persistence in high-risk patients with CML. Also elevated levels of INF α in CML groups agreed with Bütow et al. which elucidated that plasma INF α levels were considerably elevated in newly diagnosed CML patients compared to healthy controls, aligning with the current findings[25].

4. CORRELATION BETWEEN IMMUNOLOGICAL PARAMETERS

Table 4 presents the outcomes of the correlation analysis of immunological markers for this investigation, utilizing the Pearson correlation coefficient and p-value for patients. A robust correlation exists between INF α, TNF-α, and IL-6, IL-5, IL-3, IL-1 α, C3, and C5 (P=0.0001), suggesting elevated secretion of these cytokines in patients. Conversely, a weak correlation is observed between INF α and TNF-α, with a P-value of 0.025, which may reflect the intricate nature of the inflammatory milieu. The findings of the present investigation demonstrated the activation of the immune response attributed to the release of these cytokines.

Table 4. Correlation between immunological parameters in patients.

Parameters	Person correlation	IL-1 α	IL-5	IL-6	IL-3	INF α	TNF α	C3	C5
IL-1 α	r PValue	1	0.145 0.031	0.182 0.0101	0.197 0.375	0.742 0.0001	0.934 0.0001	0.277 0.043	0.104 0.021
IL-5	r PValue	0.145 0.031	1	0.344 0.047	0.236 0.056	0.811 0.0001	0.725 0.001	0.215 0.042	0.181 0.031
IL-6	r PValue	0.182 0.0101	0.344 0.047	1	0.188 0.030	0.912 0.0001	0.852 0.0001	0.227 0.038	0.194 0.011
IL-3	r PValue	0.197 0.0375	0.236 0.056	0.188 0.030	1	0.903 0.0001	0.833 0.0001	0.159 0.0305	0.188 0.042
INF α	r PValue	0.742 0.0001	0.811 0.0001	0.912 0.0001	0.903 0.0001	1	0.344 0.025	0.837 0.0001	0.904 0.0001
TNF α	r PValue	0.934 0.0001	0.725 0.001	0.852 0.0001	0.833 0.0001	0.344 0.025	1	0.971 0.0001	0.843 0.0001
C3	r PValue	0.277 0.0435	0.215 0.042	0.227 0.038	0.159 0.0305	0.837 0.0001	0.971 0.0001	1	0.218 0.030

C5	r PValue	0.104 0.0217	0.181 0.031	0.194 0.011	0.188 0.042	0.904 0.0001	0.843 0.0001	0.218 0.0301	1

The Pearson correlation coefficient among healthy subjects indicates a strong correlation between INF α and TNF-α, with a p-value of 0.0001. Additionally, moderate correlations were observed between TNF α and IL-6, IL-5, IL-3, IL-1 α, C3, and C5, with a p-value of 0.006, as well as between INF α and IL-6, IL-5, IL-3, IL-1 α, C3, and C5, with a p-value of 0.002, as presented in Table 5.

Table 5. Correlation between immunological parameters in control.

Parameters	Person correlation	IL-1 α	IL-5	IL-6	IL-3	INF α	TNF α	C3	C5
IL-1 α	r PValue	1	0.122 0.052	0.139 0.0115	0. 113 0.0110	0.742 0.0002	0.634 0.0006	0.133 0.0235	0.104 0.0217
IL-5	r PValue	0.122 0.052	1	0.344 0.047	0.147 0.046	0.611 0.0002	0.684 0.006	0.273 0.052	0.181 0.031
IL-6	r PValue	0.139 0.0115	0.344 0.047	1	0.158 0.020	0.712 0.0002	0.596 0.0006	0.155 0.034	0.294 0.031
IL-3	r PValue	0. 113 0.0110	0.147 0.046	0.158 0.020	1	0.701 0.0002	0.633 0.0006	0.221 0.041	0.178 0.032
INF α	r PValue	0.742 0.0002	0.611 0.0002	0.712 0.0002	0.701 0.0002	1	0.957 0.0001	0.737 0.0002	0.631 0.0002
TNF α	r PValue	0.634 0.0006	0.684 0.006	0.596 0.0006	0.633 0.0006	0.957 0.0001	1	0.671 0.0006	0.594 0.0006
C3	r PValue	0.133 0.0235	0.273 0.052	0.155 0.034	0.221 0.041	0.737 0.0002	0.671 0.0006	1	0.190 0.040
C5	r PValue	0.104 0.0217	0.181 0.031	0.294 0.031	0.178 0.032	0.631 0.0002	0.594 0.0006	0.190 0.040	1

The current study revealed a significant positive correlation between IL-6, IL-5, IL-3, IL-1α, C3, C5, and INFα in patients, indicating elevated cytokine secretion. Conversely, there was only a weak positive correlation between INFα and TNF-α, and a medium positive correlation between TNF-α and IL-6, IL-5, IL-3, IL-1α, C3, and C5 in healthy individuals, suggesting a complex inflammatory environment. The findings of the present investigation demonstrated the activation of the immune response resulting from the release of these cytokines. The upregulation of inflammatory cytokines IL-6, IL-5, IL-3, and IL-1α, along with their gene expression in tissue, elevated levels in blood, and serum concentrations, serve as indicators for the probability of colorectal cancer (CRC) recurrence in individuals with CRC[26]. Additionally. In comparison to controls, patients exhibited significantly elevated levels of INF α and TNF-α expression.

Cytokines influence the proliferation of all cell types in the blood and organism, hence facilitating the immune response and inflammation. The synthesis of cytokines signifies the activation of the immune response; thus, a positive correlation with certain cytokines indicates their prolific secretion by immune cells, whereas a negative correlation may result from cytokine consumption or localization within specific tissue sites, suggesting that this relationship arises from a pronounced inflammatory milieu[27].

5. CONCLUSION

IL-6, IL-5, IL-3, IL-1 α, C3 and C5 and TNF-α, INF were strongly positively correlated, however TNF-α and INF α were not correlated in CML patients. In healthy controls, there was a medium positive connection between INF α, TNF-α, and IL-6, IL-5, IL-3, IL-1 α, C3 and C5. The present study claims that elevated serum levels of immunological parameters, such as TNF-α, INF α, IL-6, IL-5, IL-3, IL-1 α, C3, and C5, in CML patients were a significant sign of a worsening of the disease and could influence the patient's reaction to chemotherapy, which could result in a detrimental outcome. Increased levels of these cytokines could be utilized as biomarkers in immunotherapy to target CML cells.

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