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Original Article

Predictive Role of Key Pro-Inflammatory Cytokines in Patients with Acute Myeloid Leukemia

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ABSTRACT

Background: Acute myeloid leukemia generates as a malignant disorder due to the aggressive proliferation of leukemic stem cells in the bone marrow and can spread into other organs. This leads to trigger immune cells to release pro-inflammatory cytokines these play a remarkable predictive role for acute myeloid leukemia progression. Objective: This study assessed the levels of certain key pro-inflammatory cytokines included interleukin-1, interleukin-6, interleukin-8, interferon-Gamma, and tumor necrosis factor-Alpha in the serum samples recovered from Iraqi patients undergone acute myeloid leukemia and analysis their predictive role in acute myeloid leukemia progression. Methods: The serum samples from peripheral blood were collected from 65 diagnosed acute myeloid leukemic patients and 25 healthy controls to measure the levels of the studied pro-inflammatory cytokines utilizing enzyme-linked immunosorbent assay. Moreover, predictive role of the tested cytokines in acute myeloid leukemia prognosis was achieved by construction of receiver operating characteristic curve. Results: The levels of the tested cytokines recorded high values among acute myeloid leukemic patients groups in compared to their corresponding controls, as a result of excessive triggering of inflammatory response by acute myeloid leukemic patients against potential injury or risk infection in order to their immunocompromised status. Tumor necrosis factor-alpha proved high accuracy for acute myeloid leukemia prediction followed by interleukin-8, interferon-Gamma, interleukin-1, and interleukin-6. Correlation between the tested cytokines was significant positive indicating that these pro-inflammatory cytokines were secreted at high levels in acute myeloid leukemic patients. Conclusion: The raising in the levels of the tested pro-inflammatory cytokines in acute myeloid leukemic patients can be aided in early prediction of acute myeloid leukemia progression. Consequently, that can be helped in improve outcomes for acute myeloid leukemic patients, specifically for those undergone sever clinical conditions.

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Keywords: Acute myeloid leukemia, Interferon, Interleukin, Predictive, Pro-inflammatory cytokines.

1 Introduction

Acute myeloid leukemia (AML) arises as a heterogeneous hematological malignancy characterized by its highly aggressive and generated by clonal expansion of hematopoietic stem cells (HSCs) and progenitor cells of the myeloid branch of the bone marrow [1]. This leads to the initiation and development of leukemic stem cells (LSCs) in the bone marrow impairing the normal operation of hematopoiesis and spread eventually into liver, spleen, lung, and other organs [2].

According to the Iraqi cancer registry issued by Iraqi cancer board in 2021, leukemia ranks the seventh place among the ten most common cancers in Iraq [3]. Moreover, the incidence rate of leukemia in 2021 is estimated 4.20 per 100,000 people distributed as 1.84 and 2.36 for males and females, respectively [3]. Besides, leukemia constitutes the fifth cancer among the top ten cancers in mortality rates in which causes the death of 666 (8.16%) of Iraqi patients in 2021 [3].

The work of immune system is highly coordinated through the critical role of cytokines network [4]. Cytokines are potent secreted proteins with small molecular weight ranged between 10 to 30 KDa which found in soluble form these mediate and regulate functions of immune cells and immune-mediated pathologies [5]. This is achieved by carrying specific information to the target cells, leading to stimulate specific response, causing cell proliferation or apoptosis [5].

In AML, cytokines have an influential role to limit the growth of LSCs either in direct pathway by induction the activities of anti-proliferative or pro-apoptotic approach or through indirect pathway by stimulating the immune cells to promote cytotoxic activity against the aggressiveness LSCs [6]. Otherwise, cytokines

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through an aberrant in their common signaling pathways can participate in a significant route in growth and survival of LSCs, independently of mutation profile of these cells [7]. Cytokines released by LSCs can implicate in hijacking of checkpoint molecules these are expressed as surface ligands on T cells like programmed cell death-1 (PD-1), cytotoxic T lymphocyte antigen-4 (CTL-4), and T cell immunoglobulin mucin-3 (TIM-3) [8]. These molecules drive regulatory pathways to prevent uncontrolled expansion of T cells these possibly facilitate oncogenic mutations [8].

Pro-inflammatory cytokines involve in the upregulation of inflammatory response against infections and injuries induced by AML and are released mainly by activated macrophages [9]. Pro-inflammatory cytokines, specifically interleukin-1β (IL-1β), IL-6, IL-8, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) are characterized during leukemic circumstances as key cytokines impact the functions of HSCs and tend to increase aggressiveness of AML [9]. Interestingly, the disregulation of pro-inflammatory cytokines network can be led to dysfunction of T cells these participate mainly in an effective anti-tumor response against LSCs [1].

The excessive production of IL-1β enables the AML progenitor cells to rapidly expand into leukemic clones that can be reduced by depletion of IL-1β receptors on the surface of LSCs [10]. The IL-6 serum levels are increased early in patients undergoing AML events and induce inflammation through upregulation of the production of neutrophils [11]. As a result, IL-6 levels are usually observed in direct correlation with relative accurate prognosis of AML occurrence [11]. Interleukin-6 promotes AML by supporting the expression of CD36 on LSCs and that can be subsequently prevented by employing IL-6 receptors-blocking antibodies [11]. Moreover, levels of IL-8 elevate during AML events which attract neutrophils to the site of infection [12]. Interleukin-8 enhances the progression of AML by preventing apoptosis of LSCs and conferring resistance to chemotherapy [12]. Interferon-γ facilitates survival of AML blasts by promoting the actively expression of the regulatory ligand, PD-1 that appeared on these cells leading to resistance to killing by effector T cells [13]. Owing to its activity in induction of certain signaling pathways, TNF-α induces rapid proliferation of LSCs and represses normal HSCs [14].

Due to their effective role in elimination or progression of AML, many recent studies focused their efforts in utilizing cytokines in clinical field by developing and manufacturing a new therapeutic as an alternative approach to chemotherapy depending on blocking the pathways by which cytokines and their receptors can be controlled [1]. In consequence, this orientation provides novel view concerning the treatment options of AML patients in the years ahead [1]. Furthermore, this approach aids in reduce the toxicity of chemotherapeutic treatment and prevents further chemotherapy dose escalation [9]. However, in spite of the greater interest in studying and analysing cytokine profiles of AML patients, the pivotal role and actual functions of cytokines in the initiation, development, and pathogenesis of AML are not fully comprehended yet [1].

This study aimed to assess serum levels of the pro-inflammatory cytokines, IL-1β, IL-6, IL-8, IFN-γ, and TNF-α in Iraqi patients these developed AML who were under chemotherapeutic treatment which could help in early prediction and rapid diagnosis of AML.

2 Materials and Methods

2. 1 Patients and Controls

In this study, 65 patients were enrolled in which verified to develop AML at different stages according to the findings ruled by specialist hematologists at center of hematology and bone marrow transplantation in Baghdad Medical City during the period from January 2024 to May 2024. The ages of patients ranged from one to 65 years distributed as 34 (52.30%) women, 21 (32.30%) men, and 10 (15.38%) children and subsequently the studied patients were divided into three groups depending on their sexes and ages: children (1-14) years, men (15-65) years, and women (15-63) years. Furthermore, three control groups were also established by contributing healthy volunteers by the total of 25 persons which relatively had the same sexes and ages of the corresponding groups of patients.

2. 2 Criteria

The inclusion criteria were included in this study obtained from the data recorded in the medical chart of patients undergone chemotherapy given their agreement or from the archive unit of the hospital and encompassed the type of acute leukemia, sex, and age for each patient. Exclusion criteria included patients developed risk microbial infections such as AIDS, HIV, and COVID-19, patients who gave hemolytic or lipemic blood samples, patients with chronic diseases such as diabetes, patients with acute thrombocytopenia, women with conditions of pregnancy, patients with deteriorating health conditions as a result of chemotherapy doses received, and others who rejected participation in this study.

2. 3 Ethics

The ethical approval 300294 granted by the ethical committee of medical research in Baghdad Medical City was relied upon to conduct this study. For adult patients, a written consent was obtained from them, but concerning AML developed children, a parental consent was obtained before releasing the details of this study.

2. 4 Collection of Samples

The samples were collected from peripheral blood for patients and controls at the volume 5 mL from adults and 2-3 mL from children using all required sterile and non-pyrogenic materials supplied from Biozek company (Holland) included tourniquet, 70% alcohol, 2% iodine, syringe, and gel and clot activator glass tubes. This process of blood collection was achieved following the rules recommended by Riedel et al. (2019) [15]. The collected blood samples in gel tubes were left in room temperature for 40 min to clot sufficiently [16]. After that, the clot was removed by centrifuging (ThermoScientific, USA) at 3000 rpm for 10 min [16].

The resulting supernant was designated serum which was immediately transferred into Eppendorf tubes (Promega, USA) and maintained under freezing (Sysmix, Japan) at -20ºC until utilizing for the serologic evaluation of the studied cytokines [16].

2. 5 Assessment of Cytokines Levels

The serum cytokines levels for IL-1β, IL-6, IL-8, IFN-γ, and TNF-α were detected by measuring their concentrations using sandwich enzyme-linked immunosorbent assay (ELISA). This test was done following the instructions of kits purchased from MyBiosource (USA). For each tested cytokine, 96 wells microtiter plate that was supplied with the kits filled with six standards, 65 patients, and 25 controls serum samples. The concentrations of the studied cytokines were determined by reading the absorbance at the wavelength 460 nm using a microplate reader (HumaReader HS, Germany).

2. 6 Statistical Analysis

The parameter data were described by applying the concept of Mean±S.E. by obtaining least significant differences (LSD) using SPSS program (version 25) following ANOVA test-one way. The statistical examination also evaluated receiver operating characteristic (ROC) curve to investigate the capacity for each studied cytokine to discriminate the true state of patients and controls [17]. Moreover, area under curve (AUC) was employed for screening the accuracy of the diagnostic tests [17]. Sensitivity was defined as the proportion of people who actually had an AML, and specificity was the proportion of controls these did not develop AML [17]. Pearson correlation coefficient test was used to determine the relationship between the studied cytokines. Statistically, the resulting differences were considered at significant effect where the p value was at ≤ 0.05 [17].

3 Results and Discussion

The findings of this study demonstrated an increasing serum IL-1β levels as significant values ($p<0.001$) were recorded among the three studied patients groups as compared to their control groups, as illustrated in Table 1. In contrast, significant differences were not found between the serum levels of IL-1β in patients of men, women and children groups. The analysis of predictive role of IL-1β in tracking of AML progression using ROC curve indicated that AUC was 0.71 with a significant difference ($p=0.009$), as shown in Figure 1. In addition, sensitivity was 81% and specificity was 40%. This result suggested that IL-1β can be used as a predicator for monitoring AML due to the high sensitivity of IL-1β. The survey conducted by Siegmund et al. (2020) [18] determined raised IL-1β levels in blood samples recovered from cancer patients receiving chemotherapy at different points of time since the occurrence of neutropenia. Furthermore, they stimulated sepsis model in which designed as an *ex-vivo* pattern by adding lipopolysaccharide from Gram negative bacteria to blood samples in order to stimulate IL-1β production and assess its level to predict its role in severity of infection. On the other hand, Sung et al. (2016) [19] evaluated single nucleotide polymorphisms in *IL-1β* encoding gene associated with bacterial infection risk in patients with AML. They clarified that genotype of *IL-1β* may provide insight into predictive mechanisms of serious infections that could be employed as a supportive-care for novel treatment module.

Table 1: Interleukin-1β serum levels of AML patients and control groups.

	Groups	Mean±S.E (pg/mL)	P value
Men	Control	994.08±71.73	<0.001***
	Patients	1620.49±61.89	
Women	Control	1076.98±78.66	<0.001***
	Patients	1522.25±49.61	
Children	Control	1088.37±48.23	<0.001***
	Patients	1398.57±53.68	
Between Patients only		-	0.56 NS

* Significant differences, NS: non-significant.

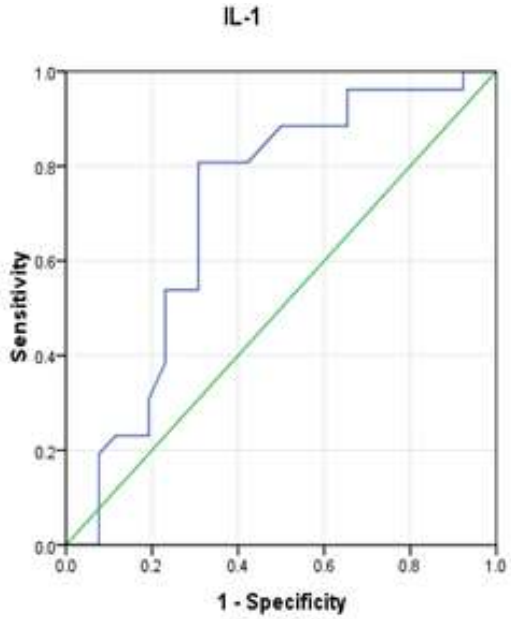

Figure 1: Receiver operating characteristic for IL-1β in AML patients and controls.

Alongside, the IL-6 levels recorded a significant increasing ($p<0.001$) in sera of patients groups in comparison to corresponding controls, as seen in Table 2. Moreover, no significant effects were noted in the serum IL-6 level in patients among men, women and children groups. The data of ROC curve for IL-6 showed that AUC was 0.6 with fair accuracy with non-significant difference, while the sensitivity was 60% and specificity was 61% (Figure 2). This finding suggested that IL-6 may use as fair but not specific biomarker for the disease in this study. The results yielded by AL-Khateeb et al. (2022) [20], Al-Maliki and Zedan (2023) [21], and Mohammed et al. (2023) [22] displayed that the levels of IL-6 were higher with significantly influence in newly diagnosed AML patients and those undergone chemotherapy. They explained that high IL-6 secretion may

affect the prediction and diagnosis of AML during the different stages of this disorder. This referred for the increasing risk of the disease progression and thus IL-6 may be utilized as a biomarker for targeting LSCs. Alongside, Urbonas and Eidukaite (2015) [23] pointed that the marker IL-6 was assessed at higher median concentrations in leukemic patients group infected with bacteremia compared to these without bacteremia. At the same time, they suggested that IL-6 concentrations during leukemic status might be applied as a further diagnostic tool, aiding in the prediction of bacteremia in patients suffered from leukemia during episodes of neutropenia.

Table 2: Interleukin-6 serum levels of AML patients and control groups.

	Groups	Mean±S.E (pg/mL)	P value
Men	Control	76.51±13.78	<0.001***
	Patients	283.27±22.85	
Women	Control	85.44±15.96	<0.001***
	Patients	221.93±16.49	
Children	Control	60.52±5.68	<0.001***
	Patients	149.35±17.28	
Between Patients only		-	0.37 NS

* Significant differences, NS: non-significant.

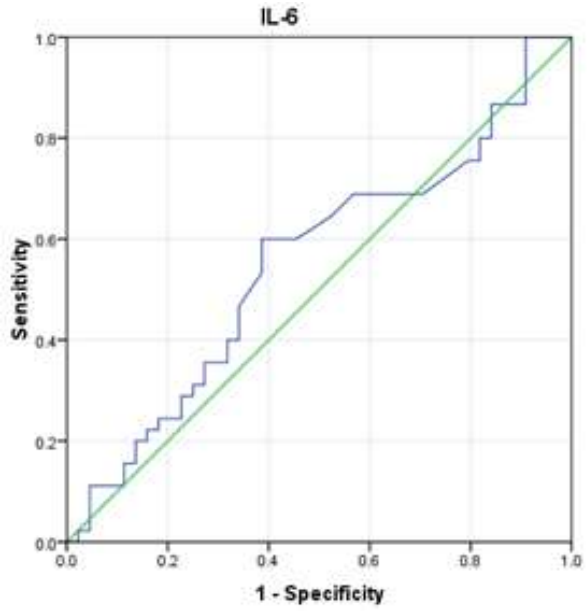

Figure 2: Receiver operating characteristic for IL-6 in AML patients and controls.

Concerning IL-8, significant escalated levels (p<0.001) in all groups of patients versus their controls were confirmed, as elucidated in Table 3. However, the differences in IL-8 levels were significant in patients from the three studied groups, especially between children patients in comparison to men patients, as well as women patients, while no effect was found between men and women patients. The analysis of predictive role of IL-8 by ROC curve revealed that AUC was 0.72 with sensitivity of 84% and specificity of 50% with a significant difference (p=0.002), as observed in Figure 3. Those results demonstrated that IL-8 could be used as a predictive biomarker according to the obtained AUC for detection the true patients as well as sensitivity of it. The result exhibited by Şahbudak Bal et al. (2017) [24] observed that IL-8 was more specific than IL-10 in determination of infections in bacteremia infected patients with neutropenia. However, Urbonas and Eidukaite (2015) [23] and Srinivasan et al. (2021) [25] recorded high serum levels of IL-8 in leukemic patients, indicating the possibility importance of this marker to predict for serious bacteremia among this immunocompromised population.

Table 3: Interleukin-8 serum levels of AML patients and control groups.

	Groups	Mean±S.E (pg/mL)	P value
Men	Control	121.41±10.18	<0.001***
	Patients	403.66±44.78	
Women	Control	121.47±19.01	0.001**
	Patients	273.96±33.46	
Children	Control	63.28±3.91 [ab]	<0.001***
	Patients	230.19±25.76	
Between Patients only		-	0.002**

a: significant differences vs. men patients, b: significant differences vs. women patients,
* Significant differences.

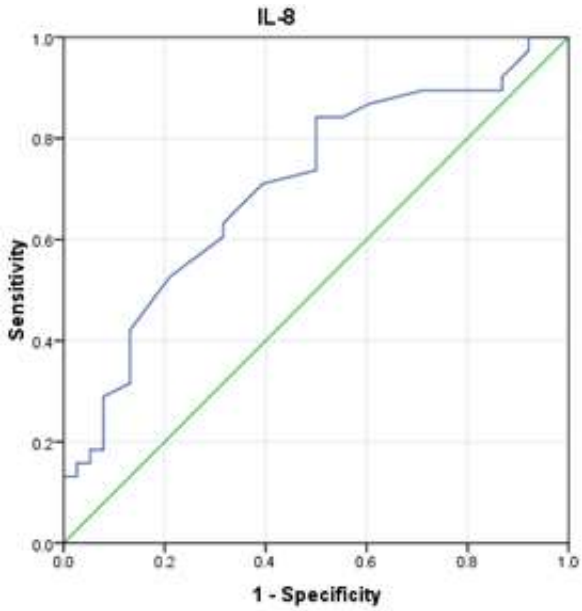

Figure 3: Receiver operating characteristic for IL-8 in AML patients and controls.

The levels of IFN-ϒ showed higher significant increase (p<0.001) in patients groups than control groups, as displayed in Table 4. Interestingly, significant differences (p<0.001) were seen in the serum IFN-ϒ level in the three patients groups, especially between

men, women, and children, as well as between patients of women and children groups. The ROC analysis showed that IFN-ϒ exhibited moderate accuracy when AUC was 0.63 with a sensitivity 96% and specificity 50% (Figure 4). However, no significant effect was found suggesting that IFN-ϒ may be utilized to help other biomarkers to detect AML severity. Sanchez-Correa et al. (2013) [26] diagnosed higher IFN-ϒ levels in AML patients and suggested that the monitoring of IFN-ϒ levels may be at direct association with disease progression, pathogenesis, and survival rate of patients. In addition, Perez-Figueroa et al. (2016) [27] studied the activity of T-helper type 1 cells by evaluating its secreted IFN-ϒ cytokine in patients with acute leukemia, founding that the circulating IFN-ϒ levels were higher in patients with significant effect than they were checked in control group.

Table 4: Interferon-Gamma serum levels of AML patients and control groups.

	Groups	Mean±S.E (pg/mL)	P value
Men	Control	60.16±4.91	<0.001***
	Patients	308.47±30	
Women	Control	118.70 ±10.91	<0.001***
	Patients	312.55±32.44 [a]	
Children	Control	146.89 ±9.92	<0.001***
	Patients	263.64±14.12 [ab]	
Between Patients only		-	<0.001***

a: significant differences vs. men patients, b: significant differences vs. women patients, * Significant differences.

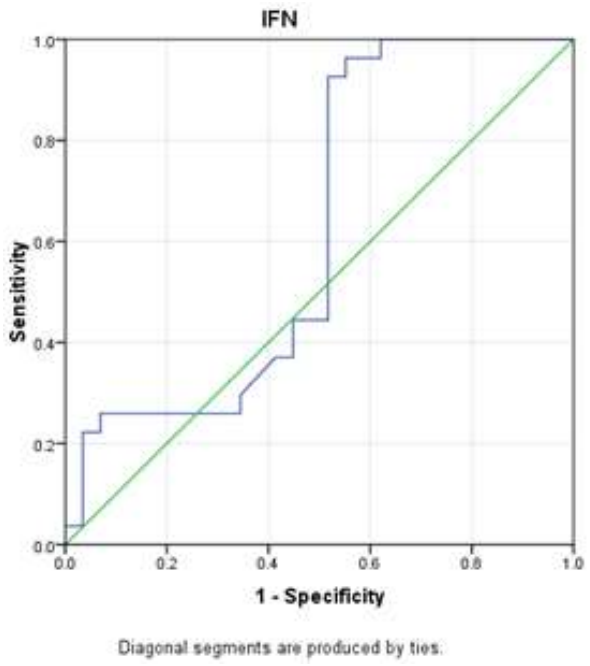

Figure 4: Receiver operating characteristic for IFN-ϒ in AML patients and controls.

The levels of TNF-α showed clear significant increases (p<0.001) in patients groups against that in controls, as seen in Table 5. However, the differences were not shown at significant form between patients among all studied groups. The results of ROC curve for TNF-α found that AUC was very high (0.99) with a significant difference (p<0.001), as the sensitivity was 100% and specificity was 97% (Figure 5). This result determined that TNF was an excellent predictor with a high accuracy to detect the patients and healthy individuals. As along with this study, Sanchez-Correa et al. (2013) [26], AL-Khateeb et al. (2022) [20], and Mohammed et al. (2023) [22] reported elevated TNF-α levels in AML patients compared with aged-matched hygienic controls. In contrast, Siegmund et al. (2020) [18] showed significantly lower TNF-α concentrations in cancer progressed patients receiving an intensive treatment course against serious effect of neutropenia they undergone. In addition, that situation may be due to the effect of chemotherapy receiving treatment [1,9].

Table 5: Tumor Necrosis Factor Alpha serum levels of AML patients and control groups.

	Groups	Mean±S.E (pg/mL)	P value
Men	Control	40.57±1.6	<0.001***
	Patients	131.61±12.18	
Women	Control	46.23±2.59	<0.001***
	Patients	113.36±8.62	
Children	Control	44.83±1.82	<0.001**
	Patients	78.51±8.01	
Between Patients only		-	0.13 NS

* Significant differences, NS: non-significant.

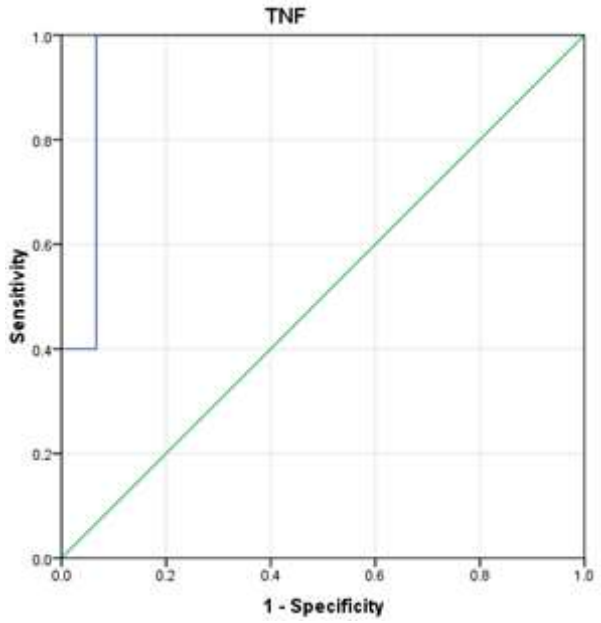

Figure 5: Receiver operating characteristic for TNF-α in AML patients and controls.

In our previous publications, the serum levels of the two microbicidal agents, nitric oxide and hypochlorite were assessed [28], in addition to three inflammatory biomarkers included C-reactive protein, procalcitonin, and lipopolysaccharide binding protein in AML patients [29]. These agents recorded raise levels in those patients who suffered from infections of Gram negative bacteria, in which the phagocytic activity and inflammatory response led to trigger the release of these agents as an innate host mechanism against bacterial infections. Thus, the investigation for the array of immunologic markers can serve as a predictive and even a diagnostic tool during leukemic conditions for modulating treatment patterns and boosting remission rate of patients, especially when they infected with risk infections [30,31].

The correlation between the studied cytokines was determined using Pearson correlation co-efficient to observe the significant relationship between these parameters in AML patients, which may be reflected a clear mechanism by which the effect of AML on inflammation process can be interpreted by the influential complementary role of these cytokines profile. The result showed that there was a significantly strong and positive correlation between the two markers, IL-1β and IL-6 (r= 0.774, p=0.001), as detailed in Table 6. Similarly, it was found that there was a significant strong positive relationship between IL-8 and IL-1β (r=0.668, p=0.001) and IL-6 (r=0.736, p=0.001). Furthermore, a significant relationship with strong and positive effect was also observed between both markers, IFN-γ and IL-1β (r=0.678, p=0.001), and IL-6 (r=0.69, p=0.001). Otherwise, a significant correlation with moderate positive association was revealed between IFN-γ and IL-8 (r=0.6, p=0.001). In addition, a significant strong positive correlation was detected between TNF-α and IL-1β (r=0.67, p=0.001), IL-6 (r=0.786, p=0.001), IL-8 (r=0.734, p=0.001) and IFN-γ (r= 0.749, p=0.001). The significant positive correlation indicated that these pro-inflammatory cytokines were secreted at high levels in AML patients because LSCs and AML blasts can produce a variety of these cytokines leading to proliferation and colony formation of AML blasts associated with reducing the antitumor response by immune cells [1,9]. This aberrant secretion of pro-inflammatory cytokines correlates with negative clinical outcomes through lowering the remission rates, high risk for AML relapse, and shorter survival of AML patients [1].

Figure 6: Correlation between the studied pro-inflammatory cytokines.

Parameter		IL-1β	IL-6	IL-8	IFN-γ	TNF-α
IL-1β	R	1				
	P value					
IL-6	R	0.774**	1			
	P value	0.001				
IL-8	R	0.688**	0.736**	1		
	P value	0.001	0.001			
IFN-γ	R	0.678**	0.690**	0.600**	1	
	P value	0.001	0.001	0.001		
TNF-α	R	0.67**	0.786**	0.734**	0.749**	1
	P value	0.001	0.001	0.001	0.001	

IL: interleukin, IFN: interferon, TNF: tumor necrosis factor, R: Pearson Correlation, * Significant differences.

Conclusion

The increased levels of the measured pro-inflammatory cytokines, encompassing IL-1β, IL-6, IL-8, IFN-γ, and TNF-α among AML patients undergone chemotherapy can be aided in prediction of AML development. This might contribute in the diagnosis of AML progression in parallel with the immunocompromised status of patients undergone chemotherapy.

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Conflict of Interest

The authors declare no conflicts of interest.

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