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Interleukin-6 level is a powerful predictor of risk for acute myeloid leukemia (AML) among Iraqi patients: A pilot study

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***Abstract*---**Background: Several studies demonstrate the existence of cytokine dysregulation in patients with acute myeloid leukemia (AML), which may be associated with pathogenesis, disease progression, and patient survival. The aim of this study was to evaluate the association of IL-6 levels and the risk of AML among Iraqi patients. Methods: A case-control study was carried out to analyze IL-6 levels in the serum of 60 patients with AML and a healthy control group. In this study, AML patients were divided into two groups: 30 AML before receiving treatment and 30 AML after receiving treatment. A variety of biochemical and anthropometric measurements, such as sex and age, BMI, serum IL-6, ALT, AST, urea, and creatinine levels, were examined in this study. Results: With regard to the patient group, the BMI, RBC, WBC, Hb, Lymphocytes, neutrophils, platelets, serum ALT, AST, urea, and creatinine levels revealed a significant difference compared with the control group. After adjustment for age, sex, BMI by multinomial logistic regression model, frequencies of high levels of IL-6 increase in total AML group (OR= 57.83, CI 95% = 9.05 – 369.21, P= 0.001), AML before receiving treatment (OR= 71.65, CI 95% = 8.05 – 637.21, P= 0.001), and AML after receiving treatment groups (OR=9.40, CI 95% = 1.49 – 59.27, P= 0.017). Conclusions: Our findings indicate that the high levels of IL-6 are associated with increased risk of AML in Iraq patients. Additionally, treatment status could influence serum levels of IL-6.

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***Keywords*---**IL-6, PCA, Odds ratio, acute myeloid leukemia, cytokine.

Introduction

Acute myeloid leukemia (AML) is a group of abnormal, uncontrolled proliferation that results in immature myeloid progenitor cells that have failed their differentiation capacity partially or completely and aggregate in the bone marrow, peripheral blood, and possibly other organs (Lo Presti et al., 2021). AML can develop in patients with an underlying hematological disease or as a result of past therapy, such as treatment with topoisomerases II, alkylating drugs, or radiation. The vast majority of the cases, it is a new cancer that arises in previously healthy individuals (Kouchkovsky et al., 2016). In the world, there are around 3 to 8 cases per 100,000 people per year (Kayser et al.,2018). AML is presently recoverable in 35 to 40 % of those 60 years of age or younger and 5 to 15 % of adults over 60 years of age, despite the fact that it was considered incurable 50 years ago (Döhner et al., 2010). Leukemia's pathogenesis are complicated and not entirely understood (Kaser et al., 2021). One of the most important components of the human immune system is the white blood cell, and AML takes down the human immune system, disrupting the overall immune system. Several studies have established a relationship between AML severity and Interleukin-6 (IL-6) (Nakase et al., 2018; Wei et al., 2021). Host defense mechanisms are largely dependent on the production of this IL-6 protein, which is activated in response to any infection or tissue damage. IL-6 is a member of the IL-1 cytokine family, and its signaling pathway is activated by IL-6Ra and gp130 (Liu et al., 2020). IL-6 is mostly released by macrophages and monocytes, but it can also be found in a variety of other tissues, including pancreatic b cells, adipocytes, fibroblasts, keratinocytes, myocytes, endothelial cells, and osteoblasts under both inflammatory and non-inflammatory diseases (Zarzeczny et al., 2018). Few studies have examined the role of IL-6 and IL-6R in the development of AML. Hematological malignancies were supported by dysregulated cytokine expression, which was also linked to resistance and relapse of AML (Kristinsson et al., 2011; Binder et al., 2018). As a result, a pilot study was designed to evaluate the association between plasma levels of IL-6 and the development of AML as essential information for the diagnosis, monitoring, and management of AML among the Iraqi population.

Materials and Methods

Study design

A pilot case-control study involved a convenience sample of 90 AML patients, 60 participants with AML (30 before starting chemotherapy, 30 or within the intensive chemotherapy) and 30 healthy controls of the same ethnicity. Cases were collected between October 2021 and March 2022 from the outpatient and inpatient departments of the middle Euphrates cancer center in the Najaf Governorate, Iraq, while controls were selected from general outpatient clinics of the same hospital while attending for minor complaints. On the basis of the global initiative for NCCN guidelines, expert physicians made the AML diagnosis (NCCN, 2020). Acute infections and other chronic diseases (such as chronic kidney or liver disease) were excluded. The study was approved by an institutional research

board of the faculty of medicine, Al-Ameed university, Iraq. All participants in the study' legal guardians signed informed consent forms with a promise of data confidentiality.

Anthropometric evaluation

Weight and height measurements were taken by experienced medical staff using standard protocols. Weight divided by height squared (kg/m^2) was used to calculate body mass index (BMI).

Sample collection and analysis

All study participants had five milliliters of peripheral venous blood obtained using plastic disposable syringes in a completely aseptic technique. Samples of blood were centrifuged at 5000 RPM for 15 minutes. Sera were stored at -20°C until immunological and clinical parameters could be determined.

Biochemical Assay

Serological tests, such as AST, ALT, urea, and creatinine levels, were performed using a conventional enzymatic method, and plasma, serum IL-6 concentration was determined using an enzyme-linked immunosorbent assay (ELISA) kit, according to the manufacturer's instructions (Cat.No.E0090Hu, Bioassay Technology Laboratory, China). The standard normal range of the kit was 7- 43.5 Pg/ml, and the sensitivity was 43.5 Pg/ml. IL-6 was measured by ELISA kit (Cat.No.E0090Hu).

Statistical analysis

The statistical significance of any differences was assessed using SPSS (version 26) in all of the reported data. The sample size was estimated using an online software formula with a 0.05 alpha error probability (P=0.05). Categorical variables were expressed as a percentage and as a frequency. The Mann–Whitney test was used to examine non-parametric data, and the median and interquartile range (IQR) were provided after the Shapiro–Wilk test was applied to ensure that the data was normal. The association between IL-6 levels and AML was tested using multivariate logistic regression analysis and presented as adjusted odds ratios (adj. OR) with a 95% confidence interval (95% CI). The R programming language (version 4.0.0) and R Studio open source were used to do the principal component analysis (PCA) (version 1.3.959).

Results

Clinical profile

A case-control association analysis was carried out of IL-6 levels in AML patients compared with healthy control individuals. The AML and control groups were well-matched for age (median = 47, IQR= 28-60, years for controls and median= 46, IQR= 33 –54, years for AML patients, but median BMI was significantly greater in the controls group (P=0.010). Median values for RBC, Hb, WBC,

Lymphocytes, Neutrophils, Platelets were lower in the AML group; however, AST, ALT, and urea levels were considerably higher in the AML group and the differences were statistically significant (p<0.001). Differences in serum creatinine levels were not statistically significant (P= 0.431) (Table 1).

Table 1: Characteristics of controls and AML patients

Variables	Controls (n=30)	AML patients (n=60)	P-Value
Age (years); median (IQR)	47 (28-60)	46 (33-54)	0.941
Sex, men (%)	8 (30%)	29 (45%)	-
Sex, women (%)	22 (70%)	31 (55%)	-
BMI (kg/m^2); median (IQR)	24.30 (22.61 – 26.22)	23.12 (21.80 - 24.47)	0.010*
RBC (10^6/µL), median (IQR)	4.80 (4.40 – 4.60)	2.61 (2.40 – 2.80)	-
Hb (g/dL), median (IQR)	13.12 (12.81 – 13.21)	8.13 (7.30 – 9.02)	<0.001
WBC (10^3/µL), median (IQR)	6.72 (6.41 – 8.41)	31.72 (22.66 – 45.13)	<0.001
Lymphocytes (%),median (IQR)	31.64 (27.61 – 34.14)	11.71 (9.04 – 12.40)	<0.001
Neutrophils (%),median (IQR)	62.20 (56.11 – 67.71)	4.51 (3.22 – 10.51)	<0.001
Platelets (%),median (IQR)	253 (222– 266.51)	46 (36.09 -58.72)	<0.001
IL-6 (pg/mL); median (IQR)	21.05 (17.09 – 29.12)	154.60 (100.12 – 178.87)	<0.001
AST (mg/dL), median (IQR)	19.83 (18.02 – 21.41)	27.10 (22.31-51.62)	<0.001
ALT (mg/dL),median (IQR)	26.24 (19.42 – 32.15)	53.41 (34.51 – 66.34)	<0.001
Urea (mg/dL),median (IQR)	31.14 (25.23 – 34.51)	53.32 (38.16 – 67.76)	<0.001
Creatinine (mg/dL),median (IQR)	0.81 (0.74 – 0.90)	0.81 (0.61 -0.91)	0.431

The values represent percentages or median (IQR) values. Significant p-values are shown in bold fonts. Abbreviations: AML: acute myeloid leukemia; BMI: Body mass index; RBC: red blood cell; Hb: hemoglobin; WBC: white blood cells; IL-6: interleukin 6; AST: Alanin aminotransferase; ALT: aspartate aminotransferase; IQR: Interquartile range

IL-6 levels and susceptibility of AML

The analysis of IL-6 levels for the four comparisons (first comparison, controls vs. total AML; second comparison, controls vs. AML patients before receiving treatment; third comparison, controls vs. AML patients after receiving treatment; and fourth comparison, AML patients before receiving treatment vs. AML patients after receiving treatment) and their respective associations with the risk of AML. After adjustments for sex, age, and BMI by logistic regression analysis, the first comparison shows great statistically significant differences for the distribution of IL-6 in normal levels vs. low levels (adj. OR = 5.25, 95% CI = 1.25–21.49, P = 0.023), and normal levels vs. high levels (adj. OR = 57.83, 95% CI = 9.05–369.21, P = 0.001).

In second, third, and fourth, comparisons there were dramatically significant differences for the distribution of IL-6 in normal levels vs. high levels (adj. OR = 71.65, 95% CI= 8.05 - 637.21, P= 0.001; adj. OR = 9.40, 95% CI= 1.49 – 59.27, P= 0.017; adj. OR = 0.10, 95% CI= 0.02 - 0.43, P= 0.002, respectively) (Table 2).

Table 2: Distribution of IL-6 levels in controls and AML subgroups

First comparison: Control vs. Total AML patients						
IL-6(pg/ml)	Controls (n=30)	Total AML (n=60)	Crude OR (95% CI)	P-Value	Adj. OR (95% CI)	P-Value
Normal levels	22 (73%)	15 (25%)	Ref.	Ref.	Ref.	Ref.
Low levels	6 (20%)	14 (23%)	3.42 (1.07 – 10.91)	0.038*	5.25 (1.25 – 21.49)	0.023*
High levels	2 (7%)	31(52%)	22.73 (4.71 -109.63)	0.001*	57.83 (9.05 – 369.21)	0.001*
Second comparison: Control vs. AML patients before receiving treatment						
IL-6(pg/ml)	Controls (n=30)	AML (n=30)	Crude OR (95% CI)	P-Value	Adj. OR (95% CI)	P-Value
Normal levels	22 (73%)	5 (17%)	Ref.	Ref.	Ref.	Ref.
Low levels	6 (20%)	3 (10%)	2.20 (0.40 – 11.94)	0.361	3.10 (0.36 – 26.73)	0.302
High levels	2 (7%)	22(73%)	48.4 (8.46 – 276.50)	0.001*	71.65 (8.05 – 637.21)	0.001*
Third comparison: Control vs. AML patients after receiving treatment						
IL-6(pg/ml)	Controls (n=30)	AML (n=30)	Crude OR (95% CI)	P-Value	Adj. OR (95% CI)	P-Value
Normal levels	22 (73%)	15 (50%)	Ref.	Ref.	Ref.	Ref.
Low levels	6 (20%)	6(20%)	1.46 (0.39 – 5.42)	0.566	1.76 (0.44 – 6.92)	0.420
High levels	2 (7%)	9(30%)	6.60 (1.24 – 34.94)	0.026*	9.40 (1.49 – 59.27)	0.017*
Fourth comparison: patients before receiving treatment vs. AML patients after receiving treatment						
IL-6(pg/ml)	AML (n=30)	AML (n=30)	Crude OR (95% CI)	P-Value	Adj. OR (95% CI)	P-Value
Normal levels	5 (17%)	15 (50%)	Ref.	Ref.	Ref.	Ref.
Low levels	3 (10%)	6(20%)	0.66 (0.12 – 3.70)	0.643	0.58 (0.10 – 3.39)	0.550
High levels	22(73%)	9(30%)	0.13 (0.03 – 0.48)	0.002*	0.10 (0.02 – 0.43)	0.002*

Significant p-values are shown in bold fonts. Abbreviations: AML: acute myeloid leukemia; Ref: Reference; IL-6 : interleukin 6; OR: odds ratio ; Adj.OR: adjusted odds ratio

Multivariate analysis

The multivariate analysis was performed using the principal component analysis (PCA) that clustered the study population into three subclasses: (1) controls and (2) AML before treating patients, (3) AML treatment patients as illustrated in (Fig.2). The axis one and two represented about 34.4% and 21.7% of the variance, respectively. With longer arrows, anthropometric and biochemical measurements were shown to have a greater effect on separation.

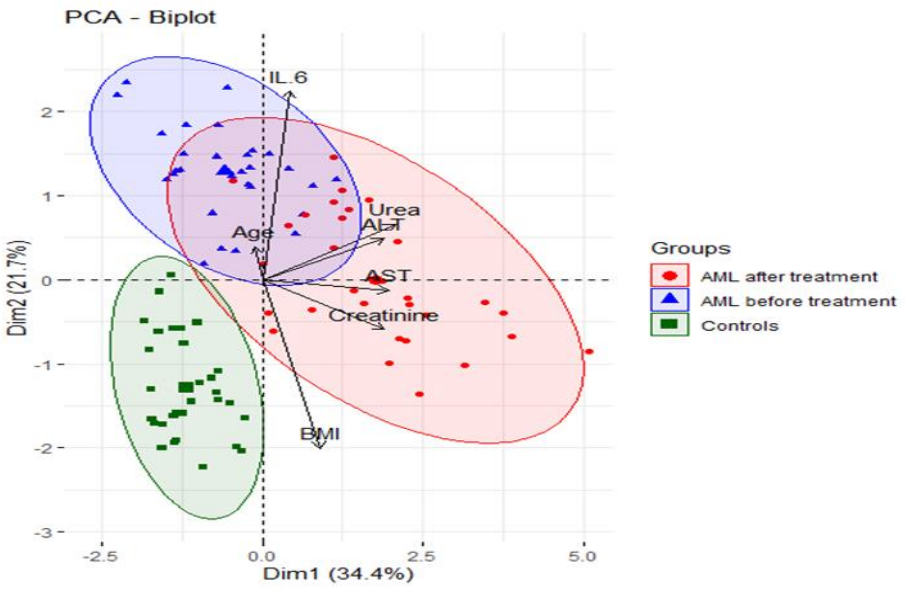

Fig1: Principal component analysis (PCA) for data evaluation. The multivariate analysis showed clustering of the study population into three classes (controls, AML patients before receiving treatment, and AML patients after receiving treatment). Dimension 1 (Dim 1) and dimension 2 (Dim 2) accounted for 34.4 % and 21.7% of the variability, respectively. The demographic, clinical and biochemical data were represented as arrows; with the longer ones indicating more impacts on the separation.

Discussion

The pathogenesis of various blood cancers, including AML, have been associated with cytokine dysregulation, and plasma cytokine levels have been linked to disease progression and survival (Tsimberidou et al., 2008; Sanchez-Correa et al., 2013). In this work, there were statistically significant differences between two studied groups regarding the BMI and clinical measures; RBC, Hb, WBC, lymphocytes, neutrophils, platelets, AST, ALT, and urea. In the current study, we observed that AML patients had lower examined complete blood counts, while BMI, liver function tests, and urea levels were higher. This is consistent with previous studies that found that AML patients had significant differences in various clinical parameters, such as liver function tests, renal function tests, and some complete blood counts, compared to healthy individuals (Alawad et al., 2016; Jongen-Lavrencic., 2018; Wei et al., 2021).

In the present study, We studied IL-6 levels among 90 Iraqi patients with AML compared to 30 matching controls. The percentage of distribution for high levels were 7%, in controls and 52%, 73%, and 30% in total AML, AML before receiving treatment, and AML after receiving treatment cases, respectively. After adjusting for age, sex, and BMI, the higher level of IL-6 was dramatically increased by 57 fold in the total AML group compared with healthy controls [OR = 57.83, 95 %CI: 9.05 – 369.21, P = 0.001]. Besides, low level [OR = 5.25, 95% CI: 1.25 – 21.49, p =

0.023], was also linked with increased risk for AML. On the other hand, under the AML before and after receiving treatment groups, there was a seventy-one and nine-times increase in the risk of AML [OR = 71.65, 95%CI: 8.05–637.21, p = 0.001; OR = 9.40, 95%CI: 1.49–59.27, p = 0.017], respectively. Recent studies also show that abnormal cytokine signaling pathways may play an important role in the development, resistance, and relapse of AML (Carey et al., 2017; Wei et al., 2021). However, the idea that inflammation plays a role in the development of cancer is now widely recognized. Nuclear factor-B (NFkB), a key player in the production and activation of a variety of pro-inflammatory cytokines in the tumor microenvironment, is one of the most important drivers of this linkage (Mitchem et al., 2013; Hou et al., 2020). Cancer cell proliferation is controlled by several pro-inflammatory cytokines generated by innate and adaptive immune cells, which supports tumor promotion and progression. IL-6 is one of these, and it is known to be unregulated in cancer. It is critical in the development of human cancer and activates carcinogenic pathways (Mihara et al., 2012).

Overexpression of IL-6 in many types of tumors, including leukemia cells, indicates that this cytokine is associated with many malignancies (Grivennikov et al., 2011). IL-6 regulates practically all hallmarks of cancer, including apoptosis suppression, proliferation, survival promotion, invasiveness, angiogenesis, and metastasis, as well as cancer cell metabolism (Kumari et al., 2016; Chang et al., 2013). As a result, similar to the association between cancer and inflammation, there is a strong association between IL-6 levels and cancer progression. To our knowledge, this is the first study to investigate the association between levels of IL-6 and the risk of developing AML in an Iraqi population. Our findings are consistent with previous studies, such as a study in Egypt that investigated the prognostic impact of increased serum interleukin-6 in AML patients and demonstrated that IL-6 levels were higher in AML patients than in healthy controls [P<0.001]. However, their sample size [80 cases and 35 controls] was close to the sample size in our study (Abd El Maksoud et al., 2010). Regarding the study of Chinese population, Wu et al noticed significant differences in the IL-6 levels in his study including 42 cases versus 36 controls (Wu et al., 2009). A study from Spain showed an increase in IL-6 levels in AML patients [P = 0.003]. However, their sample size [42 cases and 58 controls] was smaller than the sample size of AML cases in our study (Sanchez-Correa et al., 2013). Finally, our findings suggest that IL-6 has therapeutic benefits in AML.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

This work was a part of MSC project carried out in college of science, University of Kufa, Iraq. Dr. Ikhlass Ali Hussein Al-Hilaly was the supervisor on the project, while Esraa S. Al-Fatlawey was the MSC candidate, and Ali M. Omara carried out the full statistics.

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Abbreviation list

AML: Acute myeloid leukemia
IL-6: Interleukin 6
BMI: Body mass index
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
Hb: Hemoglobin
RBC: Red blood cell
WBC: white blood cell
SD: standard deviation
OR: Odds ratio
IQR: Interquartile range
PCA: Principal component analysis
NFkB: Nuclear factor-B

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