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Determination of the level of interleukin 6 in pregnant women with preeclampsia

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ABSTRACT

Introduction: Pre-eclampsia represents a potentially life-threatening condition during pregnancy that significantly contributes to maternal and neonatal morbidity and mortality. Numerous studies within the fields of obstetrics and gynecology have documented elevated concentrations of interleukin-6 (IL-6) in women diagnosed with preeclampsia, suggesting that this cytokine may play a critical role in the pathophysiological mechanisms underlying the hypertension associated with this condition.

Objectives: The aim of this investigation was to conduct a case-control study aimed at comparing the levels of IL-6 between pregnant women diagnosed with preeclampsia and those with normal pregnancies, in order to ascertain the presence of elevated IL-6 levels among the former group.

Patients and Methods: This case-control study comprised 384 pregnant women at a gestational age exceeding 20 weeks, who were already diagnosed as preeclamptic and designated as cases, alongside a control group of 384 women devoid of any signs of hypertension or proteinuria during their pregnancies, matched for maternal age, body mass index (BMI), and gestational age. For all participants, IL-6 levels were quantified using an enzyme-linked immunosorbent assay (ELISA) that employs the Sandwich-ELISA methodology for the in vitro determination of human IL-6 concentrations in serum. Additionally, hemoglobin concentration, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), white blood cell (WBC) count, and platelets count were assessed utilizing a hematology analyzer based on the Coulter Principle. Furthermore, age, body mass index, gestational age, systolic blood pressure, and diastolic blood pressure were meticulously recorded.

Results: Our findings revealed a statistically significant elevation in the levels of IL-6 among pregnant women with preeclampsia compared to those with normal pregnancy ($P < 0.001$). Moreover, IL-6 exhibited a positive correlation with diastolic blood pressure ($P = 0.001$).

Conclusion: Our study indicates that IL-6 levels are markedly elevated during pregnancy in women diagnosed with preeclampsia.

Implication for health policy/practice/research/medical education:

In women with preeclampsia, serum interleukin 6 (IL-6) may be elevated as several studies revealed this occurs due to inflammatory status during preeclampsia that stimulate IL-6 as a pro-inflammatory cytokine. Our study appears fourfold increase in preeclampsia women compared to the normal pregnant control cohort which can be as predictive marker for preeclampsia diagnosis, monitoring disease severity, and strategy for treatment through factors that work on inhibition of IL-6.

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Introduction

Pregnancy-associated hypertensive disorders persist as the predominant contributors to morbidity and mortality among both mothers and neonates (1). Pre-eclampsia constitutes a potentially life-threatening condition during gestation. This condition is characterized as a complex multisystem disorder, defined by the abrupt onset of hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) occurring after 20 weeks of gestation, accompanied by at least one additional symptom, such as proteinuria, maternal organ dysfunction, or uteroplacental dysfunction (2). The prevalence of pre-eclampsia in the studies ranged from 0.17% to 5%, exhibiting variation across different countries (3). The prevalence of preeclampsia among pregnant women in Iraq is significantly elevated in comparison to their counterparts in other adjacent developing nations (4). Despite the ambiguity surrounding the pathophysiology or primary etiology of preeclampsia, placental insufficiency has been identified as the initiating factor for this condition (5). It has been established that abnormal placentation, which leads to uteroplacental ischemia and subsequent multi-organ failure, is a significant contributor to the disease. The dysfunction of the placenta in pre-eclampsia results in endothelial impairment and the development of a proinflammatory state, leading to an imbalance in circulating angiogenic factors within maternal circulation. Furthermore, pre-eclampsia has been shown to manifest as a proinflammatory condition, evidenced by elevated levels of proinflammatory mediators, cytokines, and adhesion molecules (6). Within the context of a normal pregnancy, there is an upregulation of innate immune cells such as monocytes and granulocytes, concomitant with a downregulation of dendritic and natural killer (NK) cells. Conversely, the altered immune response characteristic of preeclampsia results in an increased production of dendritic and NK cells, thereby initiating inflammatory processes akin to those observed in autoimmune disorders. The maternal circulation of women with preeclampsia exhibits significantly diminished levels of anti-inflammatory cytokines relative to pro-inflammatory ones, such as interleukin 6 (IL-6), a disparity that exacerbates the pregnancy and fosters persistent inflammation. This IL is implicated in endothelial dysfunction within the vascular endothelium, marked by an upregulation of adhesion molecule synthesis (5). Consequently, IL-6 emerges as the most salient cytokine involved in the pathophysiology of preeclampsia; through alterations in the morphology of endothelial cells and intracellular actin filaments, IL-6 possesses the capacity to markedly enhance endothelial permeability. Moreover, IL-6 also stimulates a placenta-derived growth factor, which induces systemic vascular dysfunction and is regarded as a critical factor in the

pathophysiological mechanisms of preeclampsia (7).

Objectives

In this study, we aimed to compare the levels of IL-6 in preeclampsia pregnant women with those in normotensive pregnant women to ascertain whether there exists an elevation in IL-6 levels among preeclamptic subjects, as well as to investigate the potential association between IL-6 levels and both systolic and diastolic blood pressure.

Patients and Methods

Study design

A case-control study was conducted in the Dhi-Qar governorate located in Southern Iraq from November 2023 to April 2024, which included a total of 384 pregnant women diagnosed with preeclampsia designated as cases, in comparison to 384 healthy pregnant women serving as controls. The sample size for the cases group was determined utilizing Cochran's formula:

$$n = \frac{z^2 \times p \times q}{e^2}$$

Where ' n ' represents the sample size. ' z ' denotes the selected critical value corresponding to the desired confidence level; for the purposes of this study, a confidence level of 95% was established, which yields $z=1.96$. ' p ' signifies the estimated proportion of an attribute present within the population; in this analysis, a maximum variability assumption was made, resulting in $p = 0.5$. ' q ' is defined as $1 - p$, thus rendering $q = 1 - 0.5 = 0.5$. ' e ' represents the desired level of precision adopted in this study, set at $\pm 5\%$ precision.

The computed sample size is as follows:

$$n = \frac{(1.96)^2 (0.5)(0.5)}{(0.05)^2} = 384.16 = 384$$

Inclusion criteria and exclusion criteria

The study encompassed pregnant women who were beyond 20 weeks of gestation, having been previously diagnosed with preeclampsia by qualified obstetricians, and who regularly attended specialized hospitals and outpatient clinics as part of the study cohort.

Conversely, the study excluded pregnant women afflicted with infections, chronic inflammatory conditions, and autoimmune diseases such as rheumatoid arthritis and diabetes, as these conditions are known to induce elevated production of IL-6.

Patients' groups

Informed consent was duly acquired from all participants involved in our study for the procedures delineated within this research. Ethical approval for the study was granted by the institutional ethics committee of our university.

The diagnostic criteria set forth by the national high blood pressure education program working group report on high blood pressure in pregnancy were employed to identify cases of preeclampsia and differentiate them from gestational hypertension (8). Preeclampsia was operationally defined by the presence of systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, alongside proteinuria levels of ≥ 0.3 g/24 h or a proteinuria/creatinuria ratio of ≥ 30 mg/mmol, all occurring post 20 weeks of gestation (9). The study was conducted on a sample of 384 hypertensive pregnant women, recruited from multiple clinical centers as well as a comparable number of normotensive pregnant women serving as a control group, with both groups being over 20 weeks of gestation. The control group comprised women devoid of any indicators of hypertension or proteinuria during their pregnancies, matched for maternal age, body mass index (BMI), and gestational age with the hypertensive group. Age ranges for both cohorts spanned from 18 to 42 years, with a mean age of 28.575 ± 7.372 years.

Sampling

A volume of five milliliters of peripheral venous blood was drawn from each participant, subsequently divided into 2 milliliters in an ethylenediaminetetraacetic acid (EDTA) tube containing anticoagulants, and three milliliters in a clot activator serum separating gel tube devoid of anticoagulants. The EDTA tubes containing whole blood were utilized for complete blood count assessments via a hematology analyzer employing the Coulter Principle to quantify hemoglobin concentration, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) and also white blood cell (WBC) count, across with platelets count. The blood samples placed in the gel tube were permitted to clot for 30 minutes at ambient temperature before undergoing centrifugation for 15 minutes, after which the serum was isolated and utilized

to measure IL-6 levels, determined using the AESKULISA Human IL-6 ELISA (enzyme-linked immunosorbent assay) Kit. This ELISA kit is based on the Sandwich-ELISA methodology, designed for the in vitro quantitative assessment of human IL-6 concentrations in serum, with a cutoff value deemed normal according to both manufacturer specifications and experimental data set at ≤ 5 pg/mL. Additionally, demographic data such as age, BMI, and other pertinent clinical information necessary for determining inclusion and exclusion criteria were collected for each participant.

Statistical analysis

Data was analyzed by SPSS software version 25 (IBM, Chicago, IL, USA) using a student T-test for comparing the means of two groups, also Pearson's chi-square test was conducted to compare the frequency of qualitative variables among the different groups. The level of significance was set at $P < 0.05$ to detect significance.

Results

Table 1 presents the primary demographic and clinical attributes of the participants; there existed no statistically significant disparity in age between the preeclampsia group and the normotensive group (28.150 ± 7.645 versus 29.000 ± 7.262 years; $P = 0.720$). Moreover, no statistically significant difference in gestational age between the preeclampsia group and the normotension group was observed (29.200 ± 6.787 versus 31.350 ± 6.301 weeks; $P = 0.306$). The BMI exhibited comparability across both groups, revealing no statistically significant difference (28.255 ± 3.846 versus 26.850 ± 3.394 kg/m²; $P = 0.228$). The levels of IL-6 were found to be significantly elevated in the preeclampsia cohort compared to the normotensive group, presenting values of 16.585 ± 5.764 and 3.560 ± 1.933 pg/mL respectively ($P < 0.001$). Systolic blood pressure measurements were markedly higher in the preeclampsia group (15.000 ± 0.858 mm Hg) in comparison

Table 1. Comparison of the major clinical characteristics of women with preeclampsia and normotensive pregnant women

Parameter	Preeclampsia (n = 384)	Normotension (n = 384)	P value
	Mean $\pm$ SD	Mean $\pm$ SD	
Maternal age (y)	28.150 ± 7.645	29.000 ± 7.262	0.720 ^a
Gestational age (wk)	29.200 ± 6.787	31.350 ± 6.301	0.306 ^a
BMI (kg/m ²)	28.255 ± 3.846	26.850 ± 3.394	0.228 ^a
IL-6 levels (pg/mL)	16.585 ± 5.764	3.560 ± 1.933	$<0.001^a$
SBP (mm Hg)	15.000 ± 0.858	11.150 ± 0.812	$<0.001^a$
DBP (mm Hg)	10.150 ± 0.812	7.500 ± 0.513	$<0.001^a$
Parity n (%)			
Primigravida, n (%)	231 (60.15%)	190 (49.47%)	0.009 ^b
Multigravida, n (%)	153 (39.85%)	194 (50.53%)	

BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; IL-6, Interleukin 6.

^a Independent T-test (two-tailed), ^b Pearson's chi-square.

to the normotensive group (11.150 ± 0.812 mm Hg), while diastolic blood pressure was also significantly elevated in the preeclampsia group (10.150 ± 0.812 mm Hg) relative to the normotensive group (7.500 ± 0.513 mm Hg; $P < 0.001$ for both measurements). Regarding parity, it was observed that 231 (60.15%) of women with preeclampsia were classified as a primigravida, whereas 153 (39.85%) were identified as multigravida; conversely, in the normotensive group, 190 (49.47%) were primigravida and 194 (50.53%) were multigravida, yielding a P value of 0.009.

Table 2 presents the hematological parameters, indicating that there was no statistically significant difference in hemoglobin concentration (11.910 ± 1.051 versus 11.435 ± 1.671 g/dL; $P = 0.289$). The MCV level was found to be significantly elevated in women with preeclampsia (85.660 ± 5.374 versus 80.820 ± 7.864 fl; $P = 0.027$). Similarly, the corpuscular hemoglobin level was significantly higher in women diagnosed with preeclampsia (29.605 ± 2.057 versus 27.425 ± 3.331 pg; $P = 0.017$). Furthermore, there was no significant difference in WBC count between the two groups (8164.100 ± 2737.565 versus 7570.000 ± 2478.348 $10^9/L$; $P = 0.479$). Lastly, a significant difference was observed in platelets count (208473.900 ± 72819.941 versus 238800.000 ± 62149.734 $10^9/L$; $P = 0.165$).

Table 3 illustrates the correlation among various parameters in women diagnosed with preeclampsia, revealing a significant negative relationship between age and gestational age, as well as between MCV, MCH, and WBCs, with P values recorded at 0.049, 0.002, 0.006 and 0.011, respectively. Meanwhile, IL-6 exhibited a positive correlation with diastolic blood pressure ($P = 0.001$), while demonstrating a negative correlation with hemoglobin levels and WBC counts, yielding P values of 0.034 and 0.029, respectively. Systolic blood pressure was negatively correlated with diastolic blood pressure, with a P value of 0.045, and diastolic blood pressure also negatively correlated with platelet count, which had a P value of 0.015. MCV showed a positive correlation with MCH and WBC, and a negative correlation with platelets, with

P values of less than 0.001, 0.043, and 0.034, respectively. Additionally, MCH exhibited a negative correlation with PLT, evidenced by a P value of 0.027, while showing a positive correlation with WBC, with a P value of 0.033. Furthermore, WBC demonstrated a negative correlation with platelets ($P = 0.026$).

Discussion

Preeclampsia has been posited as a multifaceted systemic inflammatory reaction that operates within a network comprising inflammatory immune cells, the endothelium, coagulation and complement systems, metabolic disturbances, and various alterations which predominantly regulated by cytokines (10).

Our findings indicate no statistically significant difference in age between the preeclampsia cohort and the pregnant control cohorts, which aligns with the study by Kalinderis et al (11). Similarly, no statistically significant difference in gestational age between the preeclampsia cohort and the pregnant control cohorts was found, corroborating the findings of previous studies (11-13). Furthermore, no statistically significant difference in BMI between the preeclampsia cohort and the normal pregnant control cohort was seen, which is consistent with the observations of the study by Borekci et al (13), which suggesting the influence of overweight as a contributing factor to hypertension during pregnancy may be excluded in this investigation (13).

Our study showed a statistically significant difference in the IL-6 levels, which were markedly elevated in the preeclampsia cohort, exhibiting a fourfold increase compared to the normal pregnant control cohort. This elevation is consistent with findings from numerous studies (6, 14-17). The elevated levels of IL-6 are likely to exert a considerable impact on hypertension; since, experimental data have indicated that IL-6 may play a role in inducing hypertension, as demonstrated in a previous study which found that the persistent infusion of IL-6 in pregnant rats resulted in elevated arterial blood pressure (18). This interpretation is grounded on the hypothesis of an altered immune response in preeclampsia, which

Table 2. Comparison of general hematological parameters between the two groups

Parameter	Preeclampsia (n = 384)	Normotension (n = 384)	P value
	Mean $\pm$ SD	Mean $\pm$ SD	
Hemoglobin (g/dL)	11.910 ± 1.051	11.435 ± 1.671	0.289 ^a
MCV (fl)	85.660 ± 5.374	80.820 ± 7.864	0.027 ^a
Corpuscular hemoglobin (pg)	29.605 ± 2.057	27.425 ± 3.331	0.017 ^a
($10^9/L$)	8164.100 ± 2737.565	7570.000 ± 2478.348	0.479 ^a
PLT ($10^9/L$)	208473.900 ± 72819.941	238800.000 ± 62149.734	0.165 ^a

WBC, White blood cell; MCV, Mean corpuscular volume; PLT, platelets.

^a Independent T-test (two-tailed).

Table 3. Pearson's correlation between each parameter of preeclampsia women

	Parameter	Age (y)	GA (wk)	BMI (kg/m ²)	IL6 (pg/mL)	SBP (mmHg)	DBP (mmHg)	Hb (g/dL)	MCV (fl)	MCH (pg)	WBC (10 ⁹ /L)	PLT (10 ⁹ /L)
<i>r</i> value	Age	1	-0.445	-0.267	-0.431	-0.184	-0.233	-0.009	-0.647	-0.589	-0.558	0.429
<i>P</i> value	(y)		0.049	0.254	0.058	0.436	0.324	0.969	0.002	0.006	0.011	0.059
<i>r</i> value	GA	-0.445	1	0.156	0.076	0.271	-0.111	0.140	0.214	0.119	0.014	0.179
<i>P</i> value	(wk)	0.049		0.512	0.751	0.248	0.642	0.556	0.365	0.618	0.954	0.449
<i>r</i> value	BMI	-0.267	0.156	1	0.272	-0.180	0.341	0.063	0.337	0.413	0.332	-0.299
<i>P</i> value	(kg/m ²)	0.254	0.512		0.247	0.447	0.142	0.793	0.146	0.070	0.156	0.200
<i>r</i> value	IL6	-0.43	0.076	0.272	1	-0.157	0.697	-0.477	0.335	0.269	0.489	-0.399
<i>P</i> value	(pg/mL)	0.058	0.751	0.247		0.507	0.001	0.034	0.148	0.251	0.029	0.081
<i>r</i> value	SBP	-0.184	0.271	-0.180	-0.157	1	-0.453	0.017	-0.236	-0.265	-0.007	0.343
<i>P</i> value	(mm Hg)	0.436	0.248	0.474	0.507		0.045	0.942	0.316	0.258	0.976	0.139
<i>r</i> value	DBP	-0.233	-0.111	0.341	0.697	-0.453	1	-0.390	0.277	0.258	0.316	-0.537
<i>P</i> value	(mm Hg)	0.334	0.642	0.142	0.001	0.045		0.089	0.236	0.273	0.174	0.015
<i>r</i> value	Hb (g/dL)	-0.01	0.140	0.063	-0.477	0.017	-0.39	1	0.276	0.356	-0.050	-0.151
<i>P</i> value		0.969	0.556	0.793	0.034	0.942	0.089		0.240	0.123	0.833	0.524
<i>r</i> value	MCV	-0.6	0.214	0.337	0.335	-0.236	0.277	0.276	1	0.951	0.457	-0.477
<i>P</i> value	(fl)	0.002	0.365	0.146	0.148	0.316	0.236	0.240		0.000	0.043	0.034
<i>r</i> value	MCH	-0.6	0.119	0.413	0.269	-0.265	0.258	0.356	0.951	1	0.478	-0.492
<i>P</i> value	(pg)	0.006	0.618	0.070	0.251	0.258	0.273	0.123	0.000		0.033	0.027
<i>r</i> value	WBC	-0.56	0.014	0.332	0.489	-0.007	0.316	-0.05	0.457	0.478	1	-0.496
<i>P</i> value	(10 ⁹ /L)	0.011	0.954	0.153	0.029	0.976	0.174	0.833	0.043	0.033		0.026
<i>r</i> value	PLT	0.429	0.179	-0.299	-0.399	0.343	-0.54	-0.15	-0.477	-0.492	-0.496	1
<i>P</i> value	(10 ⁹ /L)	0.059	0.449	0.200	0.081	0.139	0.015	0.524	0.034	0.027	0.026	

Hb, Hemoglobin; GA, gestational age; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; IL-6, Interleukin 6; WBC, White blood cell; MCV, Mean corpuscular volume; PLT, Platelets.

suggests that endothelial injury is induced by dysregulation of cytokine expression, characterized by increased levels of pro-inflammatory cytokines (19). However, our findings diverge from those reported in the study by Borekci et al (13). This discrepancy may be attributed to the inclusion of eclampsia patients rather than solely preeclampsia patients, as well as the classification of patients into groups based on disease severity in the study conducted by this author and his colleagues (13).

Our study also showed that, the prevalence of preeclampsia in primigravida individuals is notably higher compared to those with normotension, accounting for (56.7%) of the total cohort of preeclampsia patients and (35%) of the total population of normotensive individuals; these findings are consistent with the research conducted by Faiza et al (20). Preeclampsia is particularly frequent during a woman's initial pregnancy and is less likely to manifest in subsequent gestations, which may be attributed to the suboptimal development of blocking antibodies against placental antigens in primigravida, as opposed to a more favorable response in later pregnancies. The formation of antibodies can lead to maladaptive immune responses, which inhibit trophoblast invasion into the spiral arteries; this impediment in trophoblast cell infiltration restricts the full dilation of spiral artery walls, culminating in decreased placental blood flow

and subsequent placental ischemia, thereby releasing deleterious compounds that induce oxidative stress, a condition characterized by a predominance of free radicals over antioxidants (21,22). Such oxidative stress may precipitate endothelial dysfunction, impacting all endothelial surfaces within organ blood vessels. Endothelial dysfunction is marked by a disruption in the synthesis of substances that function as vasodilators, leading to a state of widespread vasoconstriction and hypertension. If this condition is not addressed, it may exacerbate and progress into preeclampsia (21-23). There was no statistically significant difference in hemoglobin levels between the preeclampsia group and the control group of pregnant individuals, a finding that aligns with other studies (22,23). However, MCV was elevated in the preeclampsia group compared to the control group of pregnant individuals, which is also corroborated by the findings of previous authors (23,24). Additionally, MCH was also found to be higher in the preeclampsia group relative to the pregnant control group, consistent with the results of the study by Elgari et al (24). In our study, no statistically significant differences were observed in WBC and platelet counts between the preeclampsia group and the control group of pregnant individuals, which aligns with the findings of the study by Heilmann et al (23). Despite platelet counts being lower in the preeclampsia patients,

these differences did not reach statistical significance when comparing the two groups, corroborating the findings of the study by Zakai et al (25). Platelet count serves as an indicator of the coagulation status within the body (26). In our investigation, the platelet count remained within normal ranges with no discernible differences observed between the two groups studied, reflecting normal coagulation function; this discrepancy may be attributed to the routine administration of anticoagulants to pregnant women under the supervision of obstetrics and gynecology practitioners throughout gestation. (23-25).

Age exhibited a negative significant correlation with gestational age, MCV, MCH, and WBC. IL-6 demonstrated a positive correlation with diastolic blood pressure, and this positive correlation provides additional evidence of the influence of IL-6 on blood pressure, consistent with the findings of the study by in 2019 which also reported a positive correlation with diastolic blood pressure (26). Moreover, IL-6 exhibited a negative correlation with hemoglobin levels, indicating a reduction in hemoglobin concentration during inflammatory responses, as the elevation of IL-6, identified as a pro-inflammatory cytokine, may indicate an inflammatory state within the body; this finding is in accordance with the study conducted by Žák et al which identified a relationship between changes in hemoglobin levels and the concurrent emergence of comorbid conditions (27). A decline in hemoglobin (≥ 1 g/dL drop) was associated with increased odds of the concurrent development of cardiovascular diseases, hypertension, inflammation, and other cytopenias (27). Furthermore, IL-6 also showed a negative correlation with WBC. Further, systolic blood pressure demonstrates a negative correlation with diastolic blood pressure, while diastolic blood pressure also shows a negative correlation with platelets count, with a *P* value of 0.015, corroborating the findings of the study by Reddy et al (28).

Conclusion

In summary, our investigation has revealed significantly elevated levels of the pro-inflammatory cytokine IL-6 in women experiencing preeclampsia when compared to their normotensive pregnant counterparts. Furthermore, IL-6 demonstrates a positive correlation with diastolic blood pressure, indicating that inflammatory responses play a crucial role in the pathophysiology of preeclampsia.

Recommendation

It is recommended that further studies be conducted to explore the relationship between IL-6 and preeclampsia, involving a larger cohort of participants and multiple clinical centers. Our findings suggest the potential utility of IL-6 as an additional biomarker for the prediction or

diagnosis of preeclampsia.

Limitations of the study

The study did not include other proinflammatory cytokines, particularly TNF- α , IFN- γ , IL-2, and IL-8, which also elevated in women suffering from preeclampsia as some studies showed.

Authors' contribution

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Conflicts of interest

The authors declare that they have no interest in conflict.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the National University of Science and Technology, Dhi Qar, Iraq (Ethical cod No 7322). Prior to any intervention, all participants provided informed consent. The study was extracted from the M.D., thesis of Zainelabdeen Hasan Abed in the department of medical laboratory at this university (Thesis #263) the authors have fully complied with ethical issues such as plagiarism, data fabrication, and double publication.

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