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ORIGINAL RESEARCH ARTICLE

Immunological Significance of Vimentin and Leukotriene B4 in a Comparison with Anti-Cyclic Citrullinated Peptide Antibodies in Iraqi Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease, which primarily affects the joints and is characterized by inflammation of synovial joints.
Objectives: The study aimed to detect the levels of ESR, CRP, and ACCP with VIM and LTB4, and to investigate the prognostic value of these biomarkers included in the study in a comparison with ACCP as well as predict the activity of the disease.
Methods: The study was a case-control, total of 150 individuals, Rheumatoid arthritis patients were n=100; females were 84 and males were 16, and healthy controls were n=50; females were 40 and males were 10. The study was conducted at Baghdad Teaching Hospital, Rheumatology unit, between October 2023 to March 2024
Results: Findings demonstrated that ESR, CRP, ACCP, VIM, and LTB4 levels were all highly statistically significant in Rheumatoid arthritis patients compared to healthy controls, $p<0.001$. The biomarkers levels in patients group according activity of disease based on clinical disease activity index values, the levels in patients with severe activity of disease which clinical disease activity index >22 were significantly higher compared to those found in patients with moderate or low disease activity. which clinical disease activity index ≤22 and $p<0.001$, furthermore all activities categories of disease were higher levels than healthy control level.
Conclusions: The study concluded and demonstrated that ESR, CRP, ACCP, VIM, and LTB4 were potential biomarkers to differentiation between RA patients and healthy control with it were promising to predict activity of disease and response to treatments, such as methotrexate and etanercept.

Keywords: **Biomarkers; ACCP; VIM; LTB4; Rheumatoid arthritis.**

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease, which primarily affects the joints and is characterized by inflammation of synovial joints [1]. The disease's symptoms are brought on by an inflammatory response that damages tissues and organs throughout

the body [2]. The pathology of the disease process leads to destruction of the articular cartilage and ankylosis of the joints, typically, the joints of the hands, wrists, knees, and feet are affected in a symmetric fashion [3]. Rheumatoid arthritis affects people around the world at a rate of 0.5–1.0 percent; females are affected twice or three times more frequently than males [4], Rheumatoid arthritis incidence increase with age; females are higher relative to men, at a ratio of roughly 2-3:1[5]. Auto-reactive B cells, which aid in the generation of autoantibodies, and T cells, which release cytokines when activated, are both involved in the pathophysiology of RA. Anti-cyclic Citrullinated Peptide antibodies (ACCP) are a group of autoantibodies that target peptides, including IgG, IgM, and IgA isotypes. Joint degradation and an increased likelihood of disease development are associated with these autoantibodies [6]. Diseases Modifying Anti Rheumatics Drugs (DMARDs)It is synthetic chemical medications and are (DMARDs) classified as the first line of RA treatment also should be start to taken as soon as possible after diagnosis to obtain the best result [7].

The biological disease-modifying drugs (bDMARDs) are used after a poor response to synthetic DMARDs also used in combination with methotrexate [8]. which targets multiple variables, including Tumor Necrosis Factor (TNF-α) and Interleukin-6 (IL-6) [9].

Vimentin is one of the antigens involved in the pathogenesis of Rheumatoid arthritis (RA). Generation of post-translationally modified vimentin can abolish primary immunotolerance and induce disease in susceptible hosts and drive autoimmune responses in inflamed RA joints. [10]. Vimentin results in the transformation of a fine vimentin filament network across the whole cell into amorphous clusters situated around the nucleus. This condensation of vimentin at the nuclear periphery may trigger the breakdown of higher-order chromatin structures, resulting in apoptosis [11]. The high expression of vimentin is associated with immunosuppressive status. Patients with high vimentin expression were accompanied by high expression of sPD-L1, tPD-L1, and PD-1. Because Tregs and PD-1/PD-L1 play immunosuppressive roles in the microenvironment, high levels of these factors indicate an immunosuppressive status. Although the number of infiltrating $CD8^+$ T cells was similar in patients with vimentin high and low expression, the function of $CD8^+$ T cells was probably inhibited [12]. Leukotriene B4 (LTB4) is a potent inflammatory mediator derived from arachidonic acid (AA). Two G protein-coupled receptors for LTB4 have been identified a high-affinity receptor BLT1 and a low-affinity receptor BLT2 [13].

Expression of BLT1 was confirmed in type 1 helper T cells, type 2 helper T cells, type 17 helper T cells, effector CD8+ T cells, dendritic cells and osteoclasts in addition to granulocytes, eosinophils and macrophages, while BLT1-deficient showed greatly reduced phenotypes in models of inflammatory diseases, such as Rheumatoid arthritis, atherosclerosis and osteoporosis [14]. BLT2 was recently discovered. BLT2 is homologous to the BLT1 receptor but has a greater value for LTB4 and a different ligand specificity and binding profile for various BLT antagonists [15]. BLT2 (the low-affinity receptor for LTB4) expressed more strongly than BLT1(the high-affinity receptor) in actively inflamed synovial tissue [16].BLT2, a unique receptor for 5-lipoxygenase- and cyclooxygenase-1-derived lipid mediators, represents a novel target for therapies directed at treating inflammation associated with arthritis and suggests the possibility of developing a new therapy to block LTB4 in inflammatory arthritis [17] BLT1 and BLT2 Both receptors mainly couple to induce cell migration and expression was elevated in synovial tissues in Rheumatoid arthritis (RA) than in Osteoarthritis (OA) [18]. LTB4 binds to BLT1 and BLT2, but can also enter the nucleus to attach Peroxisome Proliferator Activated Receptor alpha (PPARα). PPARα is the third group of receptors for LTB4 which are expressed in nucleus and function as lipid homeostasis factors and inflammatory response

regulators [19]. The study aimed to detect the levels of VIM and LTB4 and investigate the association of these biomarkers, including a comparison with ACCP, as well as predict the activity of the disease with the response to non-biological medications methotrexate, and Biological Etanercept in Rheumatoid arthritis Iraqi patients.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

It was an analytical case-control study design, a total of 150 individuals (100) patients and (50) healthy controls. The study was carried out between October 2023 to March 2024 in Baghdad Teaching Hospital, Rheumatology Unit. Recruited patients were diagnosed according to the American College of Rheumatology (2010) (ACR/EULAR) criteria.

2.1.2 Inclusion criteria

Patients affected by Rheumatoid arthritis that were diagnosed according to the (2010) (ACR/EULAR) criteria and who were users of conventional DMARDs (Methotrexate only), or biological DMARDs (Etanercept only), or both (Methotrexate + Etanercept) and RA patients without any DMARDs for two months or more.

2.1.3 Exclusion criteria

Patients with active infections, autoimmune rheumatologic conditions other than RA, or systemic disorders, and patients with RA who are receiving DMARD medications other than methotrexate, or biological DMARDs other than Etanercept.

2.2 Patient Groups

One hundred patients were included (84) females and 16 males; their ages ranged between (19-75), and they were at the early and established phases of RA that diagnosed clinically by a consultant rheumatologist, and the diagnosis was confirmed by laboratory and radiology examinations. Four sub-groups were divided from the Rheumatoid arthritis patient groups:
First sub-group: Included (25) patients without any DMARDs for 2 months or more (Newly diagnosed). Second sub-group: Included (25) patients who used both biological DMARDs (Etanercept) with conventional DMARDs (methotrexate).Third subgroup: Included (25) patients who used biological DMARDs (only Etanercept).Fourth subgroup: Included (25) patients taken conventional DMARDs (only Methotrexate). Healthy control group: Included (50) apparently healthy individuals (40) females and (10) males; their age ranged from (19 - 75) years and matched with the patient groups in terms of age and sex.

2.3 Collection of blood samples

Five milliliters of venous blood were obtained from patients as well as controls in disposable sterile gel tubes. Blood samples were left at temperature 25ºC for thirty minutes then centrifuged at 3000 rpm for 10 minutes. The serums were collected transport to Eppendorf tube was used to serum collection and kept at -20ºC until it was time to use, then analyzed by ELISA to evaluate the ACCP levels (Elabscience) and VIM (Elabscience) and LTB4(Elabscience). C-reactive protein was quantitatively determined by using the BS-230 (Mindray) fully automated system in human serum by photometric measurement.

2.3.1. Data collections

1. Patients' questionnaire included names, ages, duration of disease, smoking, weights, heights, family history, types of treatments.
2. Body mass index measured by using height scale in meters and body weight in kilogram then calculated by the body mass index calculator according to this equation BMI=-WEIGHT(Kg)/HEIGHT(M2).
3. Determined the disease activity by the scoring method known as clinical disease activity index (CDAI).
4. Disease history and the types of medications used recently or previously.
5. Laboratory investigation (ESR).

2.4 Statistical analysis

The analysis of the results was achieved by using Microsoft Excel 2010 and Version 26 of the Statistical Package for the Social Sciences (SPSS), the mean, the standard deviation (SD), range were used to identify any statistical differences between the groups. A t-test was used however used One-way ANOVA test in the cases of sub-groups. Statistically was indicated when the p-value was < 0.05; also, graphs and tables were used for presentations of the data, regression and person correlation tests were used to create a correlation coefficient between the study's values, receiver operating characteristic curve (ROC test) was used to determinations the values of cut-off, sensitivity and specificity.

3. RESULTS

The characteristic findings of the clinical study and investigations of subjects with quantitative analysis and evaluation of VIM and LTB4 levels for prognosis of Rheumatoid arthritis and comparison with the level of ACCP in RA patients and healthy control groups.

The study design was a case - control included totally (150). Participants' age in years of patients 45.32±11.55 was statistically non-significant $p<0.05$ than age of healthy control 45.98±15.09, and was subdivided into five age groups, (19-75 years).

The highest percentage of Rheumatoid arthritis prevalence among genders in patients was females 84 (84%) and males 16 (16%). Anthropometric data for description of the groups in the study are shown in Table 1.

Table 1. Demographics and Clinical characteristics of RA

Study variables		Groups			
		Patients N = 100		**Healthy control N = 50**	
		No.	%	No.	
Genders	Males	16	16.0	10	**10.0**
	Females	84	84.0	40	**40.0**
Age (years)	≤ 35	20	20.0	16	**16.0**
	36-45	31	31.0	7	**7.0**
	46-55	31	31.0	16	**16.0**
	≥ 56	18	18.0	11	
	Mean ± SD	45.32±11.55		**45.98±15.09**	
	p < 0.05				
SD: Standard deviation, p < 0.05 Significant					

3.1 Clinical Disease Activity Index of Patients Group (CDAI)

The newly diagnosed patients are presented with the highest score, 22.04±6.17 which is significant different ($p<0.001$) from patients who received Etanercept only 16.24±5.64, the same is true when comparing the newly diagnosed with patients who received Methotrexate only; 22.04±6.17 vs 13.24±3.95. The score of patients under the combination therapy are significantly different ($p < 0.001$) from those of patients who received only Etanercept or Methotrexate only; 21.8±5.82 vs 16.24±5.64, 21.8±5.82 vs 13.24±3.95. Finally, there is a statistically significant differences ($p<0.001$) between patients who received Etanercept only with patients who receive Methotrexate only; 16.24±5.64 vs 13.24±3.95, as shown in Table 2.

Table 2. Clinical Disease Activity Index with types of treatment in RA patients

Groups	M ± SD	No. of patients	%
Newly diagnosed	22.04±6.17	25	25%
Etanercept+MTX	21.8±5.82	25	25%
Etanercept	16.24±5.64	25	25%
Methotrexate	13.24±3.95	25	25%

3.2 The medications of RA patients

The patient's groups divided according to treatment protocol in which patients used both Biological Disease Modifying Anti Rheumatic Drugs (bDMARDs) (Etanercept) with conventional Disease Modifying Anti Rheumatic Drugs DMARD (Methotrexate) 25 patients (25%), Monotherapy bDMARDs (Etanercept) 25 patients (25%) and DMARD (Methotrexate) 25 patients (25%) in comparison with Newly diagnostic patients 25 patients (25%), as shown in Table2 .

3.3 Anti-cyclic citrullinated peptide antibodies (ACCP) Levels

The Anti-cyclic citrullinated peptide antibody levels of newly diagnosed RA patients was 49.74±17.01which is significantly higher ($p<0.001$) then healthy control 15.23±2.06, as well as with patients receiving only Etanercept 33.1±16.69.

The levels of ACCP are significantly different ($p<0.001$) between patients who received both Etanercept+MTX and patients received only Etanercept 15.13±2.2 vs 33.1±16.69 and the groups received Etanercept only their level are significantly difference ($p<0.001$) from those received only Methotrexate 33.1±16.69 vs 15.3±1.11 as shown in Table 3.

Table 3. Levels of biomarkers with types of medication and CDAI in RA patients in comparison with healthy control

Groups	ACCP ng/ml	ESR mm/hrs	CRP mg/dl	Vimentin ng/ml	Leukotriene B4 pg/ml
Healthy control	15.23±2.06	7.1±1.05	1.11±0.48	56.62±8.42	14.07±12.35
Newly diagnosed	49.74±17.01	56.88±14.52	35.64±7.56	196.8±91.54	429.71±171.69
Etanercept+MTX	15.13±2.2	39.4±16.28	26.76±10.84	53.05±12.52	92.51±10.25
Etanercept	33.1±16.69	37.68±16.	19.07±5.78	156.27±52.8	368.29±133.83
MTX	15.3±1.11	27.96±11.32	16.4±7.78	60.81±8.92	101.36±4.59
Low activity of disease CDAI ≤ 9			20.5 ± 5.12		
Moderate activity of disease CDAI ≤ 22			38.29 ± 18.79		
High Activity of disease CDAI > 22 patients			93.08 ± 38.93		

3.4 Erythrocyte sedimentation rate (ESR) levels in RA patients

The healthy group shows the lowest levels of ESR in comparisons with all other groups with a highly statistically significant differences ($p<0.001$), except for groups received Etanercept + MTX vs groups received Etanercept, with statistically non-significant differences ($p >0.05$), 39.4±16.28 vs 37.68±16.62, as shown in Table 3.

3.5 C-reactive protein (CRP) levels in RA patients

The healthy group shows the lowest levels of CRP in comparison with all other groups with a highly statistically significant differences ($p<0.001$) except for groups received Etanercept and groups that received MTX; 19.07±5.78 vs 16.4±7.78, as shown in Table 3.

3.6 Vimentin (VIM) levels in RA patients

The Vimentin levels of newly diagnosed patients with RA was 196.8±91.54 show a highly statistically significant difference ($p<0.001$) than healthy control 56.62±8.42 and groups that received Etanercept+MTX 53.05±12.52, as well as with patients received only Etanercept 156.27±52.8.The groups of newly diagnosed show a highly statistically significant difference ($p<0.001$) in comparison with group received Etanercept+MTX, Etanercept and Methotrexate; 196.8±91.54 vs 53.05±12.52, 196.8±91.54 vs 156.27±52.8, 196.8±91.54 vs 60.81±8.92.The groups received Etanercept+MTX show a significantly lower levels ($p<0.001$) in comparison with Etanercept only; 53.05±12.52 vs 156.27±52.8 and the Etanercept groups with the groups received Methotrexate only show a highly statistically significant differences ($p<0.001$) 156.27±52.8 vs 60.81±8.92 as shown in Table 3.

3.7 Leukotriene B4 (LTB4) levels in RA patients

Leukotriene B4 levels of newly diagnostic patients with RA patients was 429.71±171.69 which is higher statistically significant differences ($p<0.001$) than healthy control 114.07±12.35 and the groups received Etanercept+MTX 92.51±10.25, Etanercept only 368.29±133.83 and Methotrexate only 101.36±4.59, as well as, the groups received Etanercept+MTX shows a significantly lower levels ($p<0.001$) in comparison with Etanercept only 92.51±10.25 vs 368.29±133.83 and the groups received Etanercept with the groups received Methotrexate only show a highly statistically significant differences ($p<0.001$); 368.29±133.83 vs 101.36±4.59 as shown in Table 3.

3.8 Correlation analysis of Vimentin and Leukotriene B4 with ACCP, ESR, CRP in Rheumatoid arthritis patients

The Correlation between Vimentin, Leukotriene, and ACCP in all RA Patients recorded a significant positive correlation. As shown in Table 4.

Table 4. Correlation analysis of Vimentin, Leukotriene with ACCP, ESR and CRP in Rheumatoid arthritis patients

Factors		Person Correlation	Sig (2 Tailed)
ACCP	VIM	0.769	<0.001
ACCP	LTB4	0.879	<0.001
ACCP	ESR	0.512	<0.001
ACCP	CRP	0.482	<0.001
VIM	LTB4	0.798	<0.001
VIM	ESR	0.485	<0.001
VIM	CRP	0.453	<0.001
LTB4	ESR	0.492	<0.001
LTB4	CRP	0.462	<0.001
ESR	CRP	0.824	<0.001

3.9 Receiver operating characteristics curves (ROC Test)

For comparison between Vimentin, Leukotriene and ACCP of RA and assessment of sensitivity, specificity, and cut-off values were used to show the area under the curve and p-value of each parameter. VIM presented with acceptable performance with cutoff 59.08, sensitivity 76%, specificity = 92 %, AUC= 0.891 %, P value < 0.001, while for LTB4 Cutoff 112.5, sensitivity 82%, specificity 78%, AUC = 0.801%, P value < 0.001. and for ACCP Cutoff = 17.25, sensitivity = 76%, specificity = 74 %, AUC= 0.812 %, P value < 0.001. As shown in Table 5 and Figure 1.

Table 5. Performance analysis of study parameter

Parameters	Area	P value
ACCP	0.812	0.001
VIM	0.891	0.001
LTB4	0.812	0.001

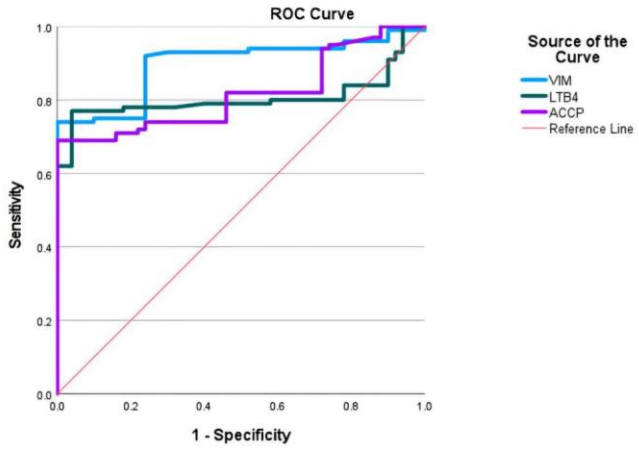

Figure 1: Receiver operating characteristics curve of VIM, LTB4 and ACCP

4. DISCUSSION

The age in years of RA patients were participants in the study was divided to groups comprising four ages groups RA greatest ages group for disease occurrence were from 19 to 75 years as seen in Table1. Increasing of the ages are in associations with diminished the body immune functions and mechanisms which causing to increase the tendency to autoimmune development [20]. Increasing the changes in B cellular compartment and the accumulations of auto reactive B cells with increasing the age which also identified as ages-associate B-cells, as well as variations in B cells receptors and genes expressions [21]. CDAI of patients without treatments the CDAI score was higher than others received treatments MTX or Etanercept, RA patients without medication due to side effects of treatments or other reasons were increased CDAI score over than patients whom received treatments [22]. Anti-Citrullinated Protein Antibodies have greater diagnostic performance in undifferentiated and early arthritis association with high sensitivity and high specificity for RA [23]. They display a great potential as a diagnostic marker for RA as they can be identified very early in RA and they may prognosticate the definitive development into RA [24]. They have also revealed the ability to discriminate between erosive and non-erosive RA disease, accordingly making them as a good prognostic sign [25]. Regarding results of ACCP level of patients was highly significant in comparison with healthy control level which was Table 3, attributed to ACCP is autoantibody specific of RA

disease diagnosis. Similarly findings from another local investigation showed ACCP level in RA patients were much greater than the healthy control [26] . The levels of ACCP in the study was changed according activity of disease and values of CDAI, ACCP mean levels in higher activity of disease patients were higher significantly than the levels in patients with moderate activity of disease and low activity, ACCP levels of all activities of RA categories were higher than healthy control.
The rise in ACCP levels in active RA patients may be due increasing citrullination and inflammation also increase immune complex formation with recruitment a lot of immune cells after complement activation with cytokines productions [27]. According to other local investigation RA patients' serum ACCP levels increased with increasing the activity of RA, higher ACCP levels were associated with higher and moderate RA severity in comparison to low activity but remain ACCP levels in all activity stages were higher than in healthy control level[28]. The difference in the levels of RA patients is mostly due to differences in disease duration, increasing ACCP level in seropositive patients were associated with increasing disease activity in 1year after diagnosis but less likely in newly diagnosis RA patients, moreover in patients with more aggressive illness course found persistence elevation of ACCP level [29]. ACCP levels in the study was affected by medication types, level of patients without medications was higher significantly than patients were taken methotrexate or patients were received Etanercept. ACCP Antibody level was dramatically decreased of serum levels in Etanercept - treated patients than in RA patients whom did not taken medications, and was changed in serum of patients taking biological DMARDs including Etanercept. Sensitivity of ACCP was 72% and specificity was 98%, according to other studies, the ACCP sensitivity was (67%) and specificity (85% - 95%) [30]. Galectins-3 are important proteins in the regulation of immune activation and inflammation [31].

Vimentin is intermediate filament protein that plays important roles in several basic cellular functions including cell migration, proliferation, and division[32]. Moreover, macrophage-like and fibroblast-like synoviocytes located in synovial joints contain abundant vimentin. These two types of cells are implicated in RA pathogenesis[33]. Also, Vimentin play an important role in the arthritogenic process as well as in RA pathogenesis [34]. Vimentin is citrullinated in RA patients, causing activation of T-lymphocytes via attaching to HLA-DR4 of antigen-presenting cells [35]. The results indicated the levels of serum Vimentin were significantly higher in (newly diagnosis group and the Etanercept group) of RA patients in comparison to the healthy control as seen in Table 3 . Also, the results showed a slight elevation in levels of serum Vimentin in patients receiving DMARDs (MTX). The results in consistent with Egyptian study showed, The serum level of vimentin in RA patients was significantly higher than in the healthy group[36]. Two previous studies reported the incidence of antibodies against vimentin from 69.7% to 81% in Mexican RA patients [37]. Other study indicates vimentin as important markers that increase in serum of RA patients and are specific for disease diagnosis [38]. The sensitivity and specificity of vimentin for RA diagnosis were 77% and 89% in comparison with healthy subjects, respectively [39].
Leukotriene B_4 (LTB_4) is known as one of the most potent chemoattractant and activators of leukocytes and is involved in Rheumatoid arthritis [40]. Several hematopoietic cell lines, monocytes, granulocytes, and lymphocytes all express the Leukotriene B4 receptors [41]. LTB4 activation triggers several functional reactions that are important to host defense, including lysosomal enzyme secretion, activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, NO formation, and phagocytosis. Additionally, LTB4 stimulates 2-integrin expression (CD11b/CD18), This impact probably connected to its capacity to promote phagocytosis and leukocyte migration. Finally, LTB4 has been shown to increase the cytotoxicity of natural killer (NK) cells. [42]. According to previous

research on inflammatory joint disease, the levels of arachidonate metabolites leukotriene B4 (LTB4) are significantly elevation in the active stage of the disease, in contrast with values obtained from healthy control and from patients during the inactive stage of the disease [43].

5. CONCLUSION

The results indicated the levels of LTB4 were significantly greater in (newly diagnosis group and Etanercept group) of RA patients in comparison to the healthy control . Also, the results showed a lower level of leukotriene B4 (LTB4) in RA patients receiving DMARDs (MTX) or mix drug (Etanercept+ MTX). These results are similar

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

E.A.H. conceptualized the study, performed the analysis, and wrote the original manuscript draft. K.I.A. contributed to data interpretation and manuscript revision. M.H.A. assisted in methodology development, literature review, and final editing of the manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was received from the College of Medicine, University of Baghdad, Iraq. In addition, the study was conducted in accordance with the Declaration of Helsinki's guiding principles.

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