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Measurement of Some Immunological Parameters (TNF-α Receptors R1, R2 and hs-CRP) and their Correlation with Crohn's Disease Activity

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Abstract **Background:** Crohn disease (CD) is a chronic inflammatory bowel disease that can lead to gradual intestinal injury and dysfunction. CD can involve patients of all ages, from children to elderly individuals and may lead to a significant mobility and to a relevant deterioration of the quality of life. **Objectives:** The main aim of this study was to investigate the serum levels and evaluate the predictive value of the immunological markers including the Tumor Necrosis Factor alpha receptors (TNF-R1, TNF-R2) and the High-sensitive C reactive protein (hs-CRP) in order to be used as a diagnostic tool for active Crohn's patient. **Methods:** The current investigation is using 140 blood samples acquired from 70 Crohn's disease patients and 70 apparently healthy individuals. A sandwich ELISA kit was used to determine serum levels of Tumor Necrosis Factor Receptors (TNF R1-R2) and high-sensitive C-reactive protein (hs-CRP) in Crohn's patient from Gastroenterology and Hepatology Hospital, Medical City in Baghdad, Iraq. **Result:** A total 140 of 1:1 ratio of the collected 70 cases and 70 controls samples were investigated respectively following inclusion and exclusion criteria. The mean level of TNF-R1 among cases and controls was (186.181±31.6085 vs. 60.773±7.6383) with significant difference of 125.4079 (t = 32.266, df:138, p = 0.000) respectively, while those of TNFR2 the mean levels group (337.846±63.2159 vs. 68.119±17.7281) respectively and the significant difference of 269.7271 (t = 34.372, df:138, p = 0.000) and in hs-CRP the mean level was (629.244±121.3586 vs. 105.357±34.1966) respectively and with significant mean difference of 523.8867 523.8867 (t = 34.764, df:138, p = 0.000). **Conclusion:** Elevated serum levels of TNFR1 and TNFR2 demonstrate strong potential as biomarkers for predicting disease activity and progression in Crohn's disease, given their roles in inflammation, apoptosis and immune regulation. However, combining these markers with hs-CRP could enhance diagnostic and prognostic accuracy, supporting a multi-marker approach for improved clinical assessment.

Key Words Crohn's Disease, Tumor Necrosis Factor Alpha Receptors, High-Sensitive C-Reactive Protein, Inflammatory Bowel Disease

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that might lead to a progressive bowel damage and impairment. The exact cause of Crohn's disease is unknown; however [1]. The illness varies in the severity and clinical course. Symptoms are variable, but usually include abdominal pain, persistent diarrhea, exhaustion, loss of appetite, weight loss and anemia, as well as extraintestinal manifestations, which can adversely influence quality of life (QoL). With There is no current remedy, CD requires ongoing management [2]. CD is considered as a worldwide health problem. Understanding the origin and pathogenesis of CD may help guide clinical diagnosis and treatment, resulting to improved clinical outcomes [3]. Patients can require persistent immunosuppression and procedures to address the disease symptoms [4]. The main aims of IBD are to control inflammation, achieve and maintain clinical remission, alleviate symptoms and improve overall quality of life for the patient [5]. Crohn's disease in the early phase can manifest with non-specific symptoms such as recurrent abdominal pain and diarrhea often mistaken for irritable bowel syndrome (IBS). This can result in a long lag from the appearance of symptoms to diagnosis, even up to several years [6]. Clinical diagnosis of CD is usually challenging due to the insidious nonspecific nature of the disease Serologic

markers have also been used in the assessment and diagnosis of Crohn's disease. However, until now there is no marker that is specific or sensitive enough to confirm or deny a diagnosis of CD [7]. in 1990 MacDonald and co-workers. reported increased TNF levels not only in rheumatoid synovial membranes but also in the mucosal and lamina propria tissues of CD patients, leading to subsequent therapeutic focus on anti-TNF strategies [8]. while hs-CRP levels can recognize low-grade systemic inflammatory conditions even without clinically apparent immunological diseases [9]. There for the current study surveyed the role of immunological markers (TNF-α receptors R1-R2, hs-CRP) in CD activity, with the goal of providing new insights into disease diagnosis and activity control. In this study, we presented a framework for understanding variations in cytokine levels, as well as presenting available information on how changing in these components causes an immunological imbalance, which may affect intern on therapeutic approaches.

Objectives

- To investigate the serum level of immunological parameters high-sensitive C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α) receptors (R1-R2)
- To compare the immunological parameters among study groups of patients with and without Crohn's
- To assess the immunological parameters as predictive markers for development of disease

METHODS

Study Setting

Samples were collected from 140 Iraqi patients divided equally between cases and controls (70 per group). While this sample size provides a practical foundation for this observational study, a formal a priori power calculation was not conducted. The 70 case patients were admitted to the hospitals after clinical confirmation with Crohn's disease from the 1st of November, 2024, to the 1st of February, 2025. The study was conducted at the Gastroenterology and Hepatology Hospital, Medical City in Baghdad. Clinically verified cases of Crohn's disease met the inclusion criteria for the case group, whereas healthy individuals free of Crohn's disease met the inclusion criteria for the control group. The exclusion criteria were patients with other inflammatory bowel disease (IBD) like Ulcerative Colitis (UC) or indeterminate colitis and patient with Gastrointestinal disease condition such as celiac disease or diverticulitis or irritable bowel syndrome (IBS).

During the hospitalization of the patient, cubital venipuncture was used to obtain blood samples (3mL). To separate the serum, the samples were put in gel tubes, allowed to clot for 15 minutes at room temperature and then centrifuged for 10 minutes at 2500-3000 rpm. Before being examined, the resultant serum was divided into five Eppendorf tubes and kept at -80°C. ELISA was then used to measure the serum levels of TNF receptors R1, R2 and hs-CRP. The biochemical laboratory was used for all laboratory analyses.

Measurement of Serum Tumor Necrosis Factor Receptors (R1-R2), hs-CRP from Patients with Crohn's Disease by Using ELISA Kit

The serum levels of TNF-R1, TNF-R2 and hs-CRP were measured using specific, commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits. Assays were performed according to the manufacturers' instructions: TNF-R1 (Biotechne No: DRT100 U.S.A.), TNF-R2 (Biotechne No: DRT200 U.S.A.) and hs-CRP (Elabscience No: E-EL-H5134 U.S.A.). All samples and standards were run in duplicate. Optical densities were measured and analyte concentrations were calculated from the standard curve.

Statistical Analysis

The collected data were processed, verified and analyzed using (SPSS) version 26 and STATISTICA version 12 software, for qualitative variables, descriptive statistics including frequency distributions, counts and percentages were applied. For quantitative data, measures such as mean, standard deviation and range were used.

To compare differences between case and control groups, an independent samples T-test was employed for quantitative variables after confirming the assumptions of normality (using the Shapiro-Wilk test) and homogeneity of variances (using Levene's test). The Chi-square test was used for categorical variables; expected cell frequencies were verified to be greater than 5.

Additionally, a univariant logistic regression model and ROC curve analysis was conducted to determine the optimal cutoff value for immunological markers TNF-R1, TNFR2 and hs-CRP as potential diagnostic predictors for Crohn's disease. A p-value of <0.05 was set as the threshold for the statistical significance in all analysis.

RESULTS

A total of 140 samples (70 cases and 70 controls) were collected in a 1:1 ratio, with each participant was screened base on inclusion and exclusion criteria. The age of participants set in from 10 to 56 years old, with significant differences among them ($x^2 = 10.467$, df = 4, $p = 0.033$) Regarding the sex, the overall sample was female dominant, with a female to male ratio of 1.25:1. There were no significant differences ($p>0.05$) between the case and control (Table 1).

Comparing the Immunological Parameters between the Groups in the Study

Considering the immunological parameters across the study's groups, it has been found that the mean level of Tumor Necrosis Factor- Receptor 1 (TNF-R1) that was significantly higher among the cases (Crohn's disease) group than that of the controls group (Table 2).

Similarly, The Crohn's disease case group had considerably higher mean values of the immunological parameter Tumor Necrosis Factor-Receptor 2 (TNF-R2) than the control group (Table 3).

Table 1: Baseline characteristics of the study's sample (n = 140)

Characteristics		Study groups (Crohn's disease)			
		Cases (Yes, n = 70)	Control (No, n = 70)	Total (n = 140)	Significancy
Age (years)	Mean±SD	29.21±10.813	34.00±11.926	31.61±11.594	t = -2.487, df = 138
	Range (min-max)	42 (13- 55)	46 (10- 56)	46 (10- 56)	p = 0.014*
Age (In groups)	< 20	13 (18.6)	11 (15.7)	24 (17.1)	x^2 = 10.467
	20-29	28 (40)	15 (21.4)	43 (30.7)	df = 4
	30-39	17 (24.3)	19 (27.1)	36 (25.7)	p = 0.033**
	40-49	7 (10)	20 (28.6)	27 (19.3)	
	≥ 50	5 (7.1)	5 (7.1)	10 (7.1)	
Sex	Female	40 (57.1)	38 (54.3)	78 (55.7)	x^2 = 0.116, df = 1
	Male	30 (42.9)	32 (45.7)	62 (44.3)	p = 0.734**

*Unpaired T-Test, **Chi-Square Test.

Table 2: Mean comparison of immunological parameter of Tumor Necrosis Factor- Receptor 1 (TNF-R1) among study's groups (n = 140)

Immunological Parameters (Mean±SD)	Study groups (Crohn's disease) (n = 140)		Mean differences	Significance*
	Cases (Yes, n = 70)	Control (No, n = 70)		
Tumor Necrosis Factor-Receptor 1 (TNF-R1)	186.181±31.6085	60.773±7.6383	125.4079	t = 32.266, df = 138 p = 0.000

*Unpaired T-Test

Table 3: Mean comparison of immunological parameter of Tumor Necrosis Factor- Receptor 2 (TNF-R2) among study's groups (n = 140)

Immunological Parameters (Mean±SD)	Study groups (Crohn's disease) (n = 140)		Mean differences	Significance*
	Cases (Yes, n = 70)	Control (No, n = 70)		
Tumor Necrosis Factor-Receptor 2 (TNF-R2)	337.846±63.2159	68.119±17.7281	269.7271	t = 34.372, df = 138 p = 0.000

*Unpaired T-Test

Table 4: Mean comparison of immunological parameter of hs-CRP among study's groups (n = 140)

Immunological Parameters (Mean±SD)	Study groups (Crohn's disease) (n = 140)		Mean differences	Significance*
	Cases (Yes, n = 70)	Control (No, n = 70)		
High-sensitivity C-reactive protein (hs-CRP)	629.244±121.3586	105.357±34.1966	523.8867	t = 34.764, df = 138 p = 0.000

*Unpaired T-Test

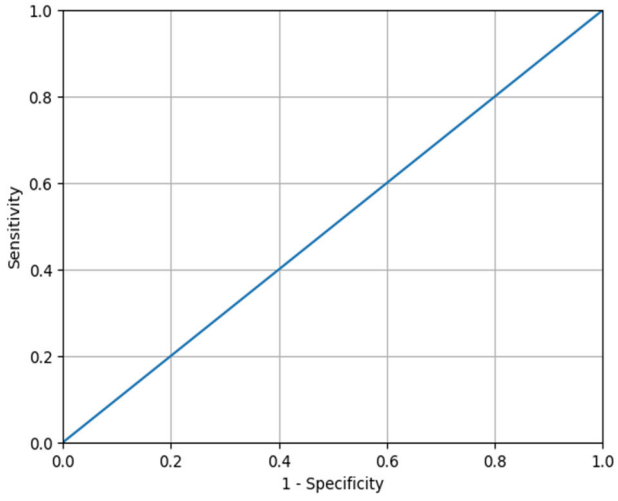

Figure 1: (ROC) curve assessing the predictive ability of Tumor Necrosis Factor-Receptor 1 (TNF-R1) as an immunological marker for Crohn's disease in the study sample (n = 140)

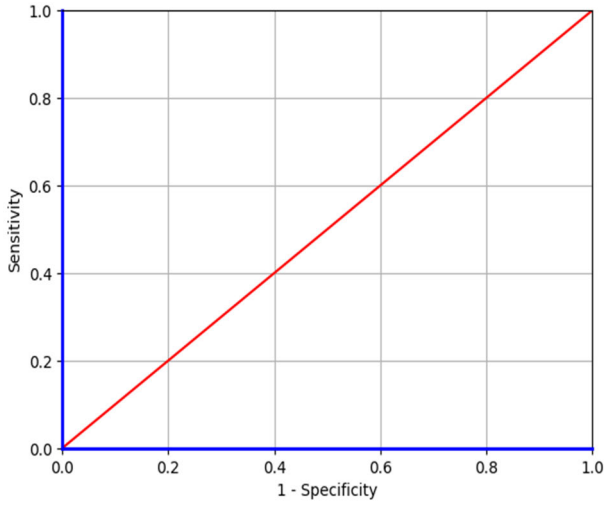

Figure 2: (ROC) curve assessing the predictive ability of Tumor Necrosis Factor-Receptor 2 (TNF-R2) as an immunological marker for Crohn's disease in the study sample (n = 140)

Likewise, the mean level of the immunological parameter of the High-sensitivity C-reactive protein (hs-CRP) was similarly considerably greater in the group with Crohn's disease than in the group without the condition (Table 4).

Immunological Parameters as Predictive Diagnostic Test

Tumor Necrosis Factor- Receptor 1 (TNF-R1) Serve as Predictive Diagnostic Test for Crohn's Diseases:

The optimal cutoff value of Tumor Necrosis Factor-Receptor 1 (TNF-R1) for identifying patients at high risk of

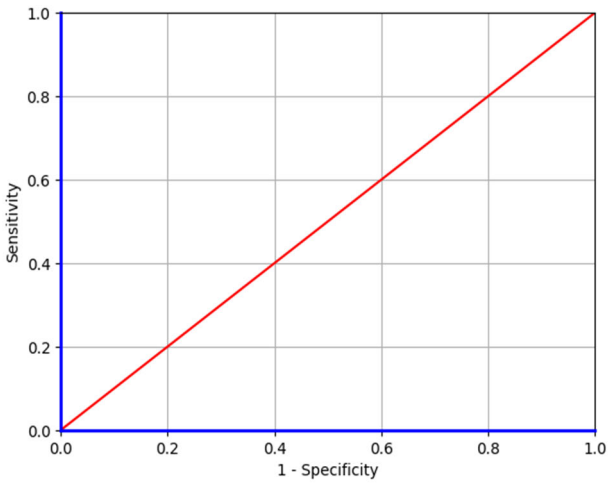

Figure 3: ROC Curve of Crohn's diseases predicted by immunological parameter of High-sensitivity C-reactive protein (hs-CRP) among study's sample (n = 140)

developing Crohn's diseases was determined to be 74.550 in a study sample of 140 participants (Figure 1).

The model demonstrated perfect sensitivity (100%) and accuracy (100%), along with high specificity (98.6%). The area under the curve (AUC) was 1.00, indicating excellent diagnostic performance (p-value = 0.000).

Tumor Necrosis Factor- Receptor 2 (TNF-R1) as a Diagnostic Predictive Marker for Crohn's Diseases

Similarly, in the optimal cutoff value of Tumor Necrosis Factor- Receptor 2 (TNF-R2) for identifying patients at high risk of Crohn's diseases was 138.150 (Figure2).

The model Achieved perfect sensitivity (100%) and accuracy (100%), along with high specificity (100%) The area under the curve (AUC) was 1.00, demonstrating ideal diagnostic performance (p-value = 0.000).

High-Sensitivity C-Reactive Protein (hs-CRP) as Predictive Diagnostic Test for Crohn's Diseases

Likewise, High-sensitivity C-reactive protein (hs-CRP) a cutoff value of 266.050 was found to most accurately identify high-risk Crohn's disease patients (Figure 3).

The biomarker demonstrated perfect diagnostic performance with 100% accuracy, 100% sensitivity, 100% specificity and an AUC of 1.00 (p-value = 0.000).

DISCUSSION

This part discusses and explains the meaning of the study's results, going beyond just presenting the numbers to show why they matter for both science and patient care. by carefully studying this set of markers and understanding how disease outcome develops.

A study by Borowitz [10] suggested That while CD is predominantly a disease of young adults, it can occur at any age and approximately 25% of patients with IBD will present before 20 years of age. This suggestion matches the result measured in this study that most of the sample at the age group of 20-29 years old (30.7%). The mean age of cases group was 29.21±10.813 years old mostly at the age group of 20-29 years old (40%) and that of controls was 34.00±11.926 years old mostly at the age group of 40-49 years (28.6%) with significant mean differences among them (t = -2.487, df = 138, p = 0.014) as well as significant differences were identified regarding age groups of study samples (x^2 = 10.467, df = 4, p = 0.033). The sex was also determined, indicating that female dominant sex with female to male ratio of 1.33:1 (57.1%; 42.9%) and 1.18:1 (54.3%; 45.7%) respectively without significant differences (p >0.05). this was supported by Xu *et al.* [11], in a large western-based study had 16-47% higher CD risk among females compared with men in the same groups.

Cytokines played a key role in the inflammatory cascade and are therefore considered to be heavily involved in the pathological process as Li and Shi [12] reported that the traditional theory of the pathogenesis of CD, is caused by immune system dysfunction and belong to Th1 cytokines mainly responsible for the development of CD. However, only some of them can be used in the treatment of CD, including TNF-α and IL6. This explains the increased levels of TNF-α receptors and hs-CRP.

Tumor Necrosis Factor (TNF) is a member of TNF superfamily [13], which carries out multiple functions through binding to cell membrane receptors TNFR-1 and TNFR-2. TNFR1 signaling pathway is crucial for granuloma formation. However, in CD, this same TNFR1 pathway become harmful. Overproduction of TNF by intestinal epithelium or by myeloid and T-cells can result in the onset of CD symptoms [14]. Data on baseline TNF-R1 concentration were available for 70 patients which has been found that the mean level of Tumor Necrosis Factor-Receptor 1 (TNF-R1) was significantly higher among cases group (Crohn's disease) than that of the controls group (186.181±31.6085 vs. 60.773±7.6383) with significant difference of 125.4079 (t = 32.266, df = 138, p = 0.000) respectively.

In TNFR2, Atretkhany *et al.* [14] found that it is associated with cellular proliferation and survival, has recently been of significant interests for its role in the maintenance of T-reg cell compartment but also in case of cancer, TNFR2 modulate immune response through enhancing function of regulatory T-lymphocytes. Therefore, drugs that activate TNFR2 are being tested a treatment. In other words, gut health balances limit the inflammatory-regulatory pathways. When disruptions occur as in commensal microbial forces, then the immune response loses its balance and is now inclined towards a pro-inflammatory position- resulting in chronic inflammatory stress [15]. Tumor Necrosis Factor- Receptor 2 (TNF-R2) was also significantly higher among cases group of Crohn's disease as compared to controls group (337.846±63.2159 vs. 68.119±17.7281) respectively with significant difference of 269.7271 (t = 34.372, df = 138, p = 0.000).

In a study proposed by Owczarek *et al.* [16], where plasma levels of TNF-R1 and TNFR2 were measured in 55

consecutive patients with CD and 41 healthy controls. The association of these markers was assessed with other inflammatory markers, disease activity and location, type of treatment and complication. The study results show a positive correlation observed between CD activity and TNFR2 levels ($r = 0.42$ for both, $p < 0.01$). a correlation between TNFα levels and CD activity was also observed $r = 0.29$, $p < 0.05$). in CD patients higher TNFα and TNFR2levels were demonstrated in those who develop complications. But the study concluded that TNFR2 are more sensitive than TNFα in the assessment of disease activity in patients with CD. Higher TNFα and TNFR2levels were demonstrated in those who develops complications. This study supports our finding in TNFR1, TNFR2 increased levels.

Regarding highly sensitive C-reactive protein (hs-CRP), an acute-phase protein, its measurement is commonly employed to diagnose and monitor inflammatory conditions like sepsis, trauma and cancer [17]. The current study showed that the mean level of immunological parameter of High-sensitivity C reactive protein (hs-CRP) was also significantly higher among Crohn's disease group than that of Crohn's disease-free group (629.244±121.3586 vs. 105.357±34.1966) respectively with significant mean difference of 523.8867 ($t = 34.764$, $df = 138$, $p = 0.000$). This role of hs-CRP in detecting subclinical inflammation is further supported by Ji *et al.* [18], who emphasized that the highly sensitive C-reactive protein has been attracting growing interest for assaying of low-grad systemic inflammation and the prediction of proneness to inflammatory disease development as a sensitive biomarker indicating subclinical immune-mediated inflammatory activity. Our study reveals that use of high-sensitive C-reactive protein provides various advantages as a prognostic and predictive marker in Crohn's disease since it can Fastly evaluated in blood, this make it accessible and less invasive biomarker when compared to endoscopic or histological examination and this was agreed by Sands [19] that at present a variety of biomarkers may assist in the determination of disease activity status in an IBD patient. These involve hematological markers, being C-reactive protein. There for the use of TNF-α receptors together with hs-CRP was determined on variety of aspects including the pathophysiological function and specificity.

CONCLUSIONS

According to previous study results, elevated serum levels of Tumor Necrosis Factor Receptor-1 (TNFR1) were observed, which is associated with its known function in apoptotic and inflammatory signaling. This provides support to its possible application as a biomarker for evaluating Crohn's disease activity. A quantifiable measure of immune activity can be obtained by quantifying TNFR1 in blood samples. Tumor Necrosis Factor Receptor-2 (TNFR2) serum levels were also markedly increased. TNFR2's significance in the disease process is highlighted by its involvement in pro-inflammatory signaling, immune regulation and tissue repair. However, combining these markers with other demonstrated indicators could enhance their predictive value for the course of the disease. Thus, this study strongly suggests using TNFR1 and TNFR2 together with high-sensitivity CRP (hs-CRP), as it is a sensitive indicator of systemic inflammation, hs-CRP may help predict possible complications in Crohn's disease, monitor treatment response and provide a more thorough evaluation of disease activity.

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Ethical Statement

This study approved by the Ethics Committee of AL-Iraqia University, Baghdad, Iraq (No. FM.SA.182). all participants were informed about the study and provided written consent before participation.

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