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A Relationship of Ficolin-3 with a Number of Anthropometric Measurements in Iraqi Rheumatoid Arthritis Patients with and without COVID19

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ABSTRACT— Anti-inflammatory intermediaries like Ficolin-3 (FCN-3) have a central function in the disease regulation of rheumatoid arthritis (RA). This study was designed to explore the relationship between FCN-3 and cert anthropometric measurements in RA patients with and without COVID19 and to investigate whether there are any correlations between FCN-3 with a Number of Anthropometric measurements. The study comprised 28 patients with RA and 28 of who infected with COVID-19 previously diagnosed with RA and 28 age- and sex-matched healthy control subjects (HCs). FCN-3serum concentrations were estimated by ELISA. The width of waist (W.W), hip (W.H), thorax (W.T) and neck (W.N) were calculated, along with body mass index (BMI) for all subjects. Ficolin-3 serum concentrations were significantly greater in patients with RA and RA with Covid-19 patients Nevertheless, RA patients and RA with Covid-19 patients showed lower levels of high-density lipoprotein (HDL). Elevated serum concentrations of FCN-3 were found to be positively associated with waist to hip ratio (W/H), waist to thoracic ratio (W/T), waist to neck ratio (W/N), ESR, while raised serum concentrations of FCN-3 were positively related with W/H, W/T, SBP, DBP, creatinine and total cholesterol (TC). FCN-3 exhibited the highest ROC curve value in comparison to other studied markers. Serum Ficolin-3 levels can be used as a novel biomarker in the detection of RA and may be an effective biomarker in the diagnostic test of RA.

KEYWORDS: ficolin- 3, rheumatoid arthritis, Covid-19, anthropometric measurements.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial cell proliferation and lymphocyte infiltration, which leads to articular gristle loss and bone degradation [1]. Previous studies on the blood of RA patients shows clear evidence of the presence of ficolin-3 level was significantly elevated in patients suffering from RF with and without rheumatic heart disease (RHD) in comparison with HCs [2].

COVID-19, which stands for coronavirus illness 2019, was designated by the World Health Organization in February 2020. SARS coronavirus 2 is the virus that causes COVID- 19 (SARS-CoV-2). COVID-19 has a wide clinical spectrum, ranging from asymptomatic carriers to severe respiratory failure needing critical care unit support (ICU). A dysregulated immune response, characterized by a decrease in suppressor T cell counts, excessive release of pro-inflammatory cytokines, and activation of several inflammatory cascades, including the contact activation, coagulation and complement cascades, contributes to the observed organ dysfunction in the latter situation [3]. After opsonization of pathogens and dying cells, the complement system serves as a first line of defense, triggering an inflammatory reaction [4].

At least three pathways, namely the classical, lectin and alternative pathways, are involved in the

complement cascade. After binding of complement's pattern-recognition receptors (PRR), such as mannose binding lectin (MBL) and ficolins, to carbohydrate patterns, acetyl groups, or immunoglobulin M, MBL-associated serine protease (MASP)-1 and -2 is activated and the C3 convertase is assembled [5].

Ficolins are a type of pattern-recognition protein that aids the complement system in its function. Ficolin-1 (M ficolin), ficolin-2 (L ficolin) and ficolin-3 (H ficolin) are the three types [6]. Ficolin-3, the most common ficolin in circulation, is produced mostly in the liver and lungs [7]. Infectious and autoimmune illnesses have been linked to ficolin gene variants in research [8].

Ficolin-3 concentrations in severe COVID-19 in Asian patients with considerable renal illness were shown to be higher in a limited research [9]. Obesity is diagnosed by anthropometric measures of body mass index (BMI), which is computed as weight in kilograms divided by square of height in meters (kg/m2) and is described as an increase in fat at a significant level to induce adverse health implications [10].

Overweight/obesity is linked to a high frequency of chronic autoimmune and inflammatory diseases, such as type 2 diabetes and rheumatoid arthritis, as a pandemic public health crisis in the Western world, resulting in significant social and economic consequences [11]. More than 60% of RA patients are overweight or obese, according to earlier figures (BMI 25 kg/m2) [12]. Furthermore, even from the onset of RA, obesity is a significant and growing comorbidity [13].

2. METHODS

The participated in the study included 56patients, 28 patients with RA and of whom infected with COVID-19 previously diagnosed with RA who were present at the Unit of Rheumatology at the Al-Fallujah teaching Hospital and Al-Shifaa Hospital (Anbar, Iraq), from November 2021 to February 2022 were enrolled on the study, using the American Rheumatism Association's 1987 revised principles for the classification of RA [14], For the purpose of comparison, 28 (14males and 14females) control subjects were registered with no history of any rheumatic, the age ranges from 35to 65years. Demographic data and AMs of patients with RA and healthy controls (HCs) were collected. Weight was estimated to the near 0.1 kg sans shoes, socks, large clothing and extra accessories. Height was estimated to the near 0.01 m sans shoes and socks by a stadiometer. BMI (kg/m2) was calculated as weight (kg) section divided by height (m) squared. Especially AMs were examined like width of neck, width of hip, width of waist and width of thoracic (cm). To determine the concentration of FCN-3 in the subject, we used ELISA kits manufactured by the Bioassay Technology Laboratory (China) with a Thermo Scientific Varioskan microplate reader system. Other biochemical parameters in the study were determined using commercially available kits.

2.1 Statistical Analysis

Statistical analyses were conducted using SPSS version 24 and GraphPad prism version7. The statistical importance level was set at P value less than 0.05. Descriptive statistics consisting of mean and standard deviation (SD) were calculated for each parameter. Comparisons among RA cases and HCs were computed using the one way ANOVA test. The associations between AMs and the FCN-3 characteristics of both RA cases and HCs was studied via Pearson's correlation (r=−1 to 1). A receiver operating characteristic (ROC) curve was created to examine the levels FCN-3 among healthy individuals and patients group.

3. RESULTS

Data of this study showed, the mean ages (Years) of RA patients with Covid-19, RA patients and HCs were (52.14 ± 9.536), (49.68 ±9.432) and (48.54 ± 10.29) years (p=0.3727) respectively. AMs and other characteristics of all subjects are presented in (Table 1, Fig 1). The mean BMI (kg/m2) was higher among

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RA patients with Covid-19, RA Patients and HCs were (31.57 ± 2.947), (30.94 ±3.807) and (24.33 ± 1.647) respectively. BMI has shown significant differences (P< 0.0001), as shown in (Table 1, Fig 2), the mean W/H showed non-significant difference in RA patients with Covid-19, RA patients and HCs were (P=0.0007), as shown in (Table 1, Fig 3), W/N shown significant differences (P=0.193) P= 0.4784), as illustrated in the (Table 1, Fig 4) and W/T presented non-significant difference (P=0.4784) between RA patients with Covid-19, RA patients and HCs, as shown in (Table 1, Fig 5).

The results demonstrated that the mean W/H, W/N and W/T of RA patients with Covid- 19, RA patients and HCs were (1.04± 0.07157), (0.9771± 0.08254), (0.9389± 0.124) and (2.57± 0.2666), (2.501 ± 0.2267), (2.358 ± 0.3378) and (1.044 ± 0.07481), (1.04 ± 0.07566), (1.016 ± 0.1178) respectively, there were significant difference in mean blood pressure (mmHg) in both SBP (P= 0.0003) , DBP (P= 0.090) and ROP (1/Min) (P= 0.0049) The SBP, DBP, ROP levels of RA patients with Covid-19 and RA patients were significantly higher than those of HCs (132.6 ±19.3), (129.5 ± 14.94), (117.3 ± 5.179) and (89 ±19.85), (87.21 ±14.87), (77.5 ± 5.358) and (84.71 ± 7.586), (82.68 ± 6.366), (78.54 ± 6.957) respectively. shown in (Table 1, Fig 6, 7 and 8), there were significant difference in Total cholesterol and TG (mg/dL) in both T.Cho (P=0.0080) and TG (P<0.0001)

The Total cholesterol and TG levels of RA patients with Covid-19 and RA patients were moderately higher than those of HCs (187.7± 28.23), (179 ±38.61), (161.6 ± 24.64) and (188.6 ± 51.05), (174.2 ± 57.74), (118.5 ± 24.44) respectively. shown in (Table 1, Fig 9 and 10). there were non-significant difference in LDL and VLDL (mg/dL) in both LDL (P=0.0053) and VLDL (P<0.0001). The present study also showed that the levels of LDL and VLDL were non-significantly higher in RA cases than in HCs (120.9 ± 28.17), (104.9 ± 39.08), (92.14 ± 28.22) and (37.73 ± 10.21), (34.84 ±11.55), (23.69 ± 4.889) respectively. shown in (Table 1, Fig 11 and 12)

Finally, the current study demonstrated that patients with RA with Covid-19 and RF patients have significantly higher level of FCN-3 (ng/mL) than those seen in HCs (P<0·001). (2011 ± 710.5), (1241 ± 345.4) and (449.1 ± 152.1). shown in (Table 1, Fig 13)

Table 2 shows the correlations of FCN-3 with the studied parameters of both patients and control groups. From this table we can see that there is a significant association between FCN-3 and T.cholesterol, Triglycerides, LDL, VLDL, BMI, W/H, SBP, D BP and ROP (r=0.312; p=<0.01), (r=0.462; p=<0.01), (r=0.344; p=<0.01), (r=0.462; p=<0.01), (r=0.518; p=<0.01), (r=0.328; p=<0.01), (r=0.275; p=0.01), (r=0.4135; p=<0.01), (r=0.4195; p=<0.01) respectively.

Table 1. Clinical and Anthropometric Characteristics of Control, RA and RA with Covid-19 Patients.

Parameter	Controls		RA Patients		RA with Covid19		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age Years	48.54	10.29	49.68	9.432	52.14	9.536	0.3727
T.Cho. mg/dL	161.6	24.64	179	38.61	187.7	28.23	0.0080
TG mg/dL	118.5	24.44	174.2	57.74	188.6	51.05	<0.0001
HDL mg/dL	45.77	10.65	39.29	13.41	29.09	6.28	<0.0001
LDL mg/dL	92.14	28.22	104.9	39.08	120.9	28.17	0.0053
VLDL mg/dL	23.69	4.889	34.84	11.55	37.73	10.21	<0.0001
BMI kg/m^2	24.33	1.647	30.94	3.807	31.57	2.947	<0.0001
W/H	0.9389	0.124	0.9771	0.08254	1.04	0.07157	0.0007

W/T	1.016	0.1178	1.04	0.07566	1.044	0.07481	0.4784
W/N	2.358	0.3378	2.501	0.2267	2.57	0.2666	0.0193
SBP mmHg	117.3	5.179	129.5	14.94	132.6	19.3	0.0003
DBP mmHg	77.5	5.358	87.21	14.87	89	19.85	0.0090
ROP 1/Min	78.54	6.957	82.68	6.366	84.71	7.586	0.0049
D of RA Years	////	/////////	6.5	5.647	8.607	5.698	0.1703
Ficolin-3 ng/mL	449.1	152.1	1241	345.4	2011	710.5	<0.0001
D-Dimer ng/mL	-------	-------	-------	-------	2042	678.7	-------
Ferritin ng/mL	-------	-------	-------	-------	815.7	254.3	-------

Table 2. Correlation of Ficolin-3 with other parameters in the study

Parameter	Ficolin-3 ng/mL (r)	p-value
T.cholesterol mg/dL	**0.312**	**<0.01**
Triglycerides mg/dL	**0.462**	**<0.01**
HDL mg/dL	**-0.531**	**<0.01**
LDL mg/dL	**0.344**	**<0.01**
VLDL mg/Dl	**0.462**	**<0.01**
Age Years	**0.097**	**0.380**
BMI kg/m^2	**0.518**	**<0.01**
W/H	**0.328**	**<0.01**
W/T	**0.093**	**0.398**
W/N	**0.017**	**0.877**
SBP mmHg	**0.275**	**0.011**
DBP mmHg	**0.4135**	**<0.01**
ROP 1/Min	**0.4195**	**<0.01**

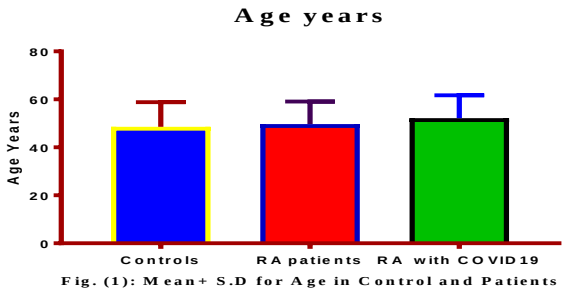

Fig. (1): Mean+ S.D for Age in Control and Patients

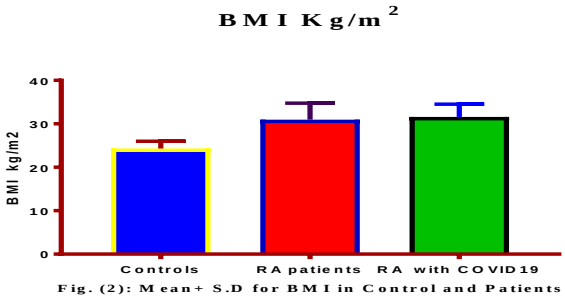

Fig. (2): Mean+ S.D for BMI in Control and Patients

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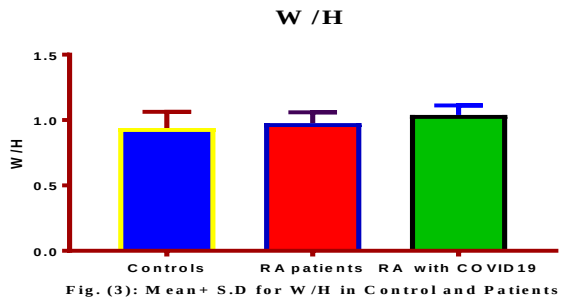

Fig. (3): Mean+ S.D for W/H in Control and Patients

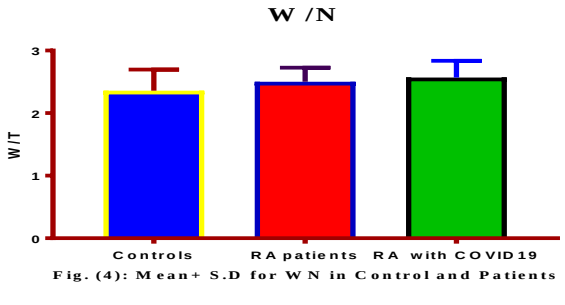

Fig. (4): Mean+ S.D for W N in Control and Patients

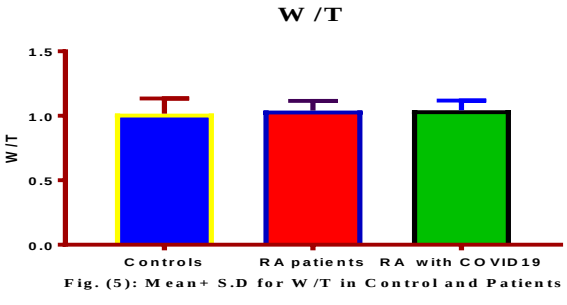

Fig. (5): Mean+ S.D for W/T in Control and Patients

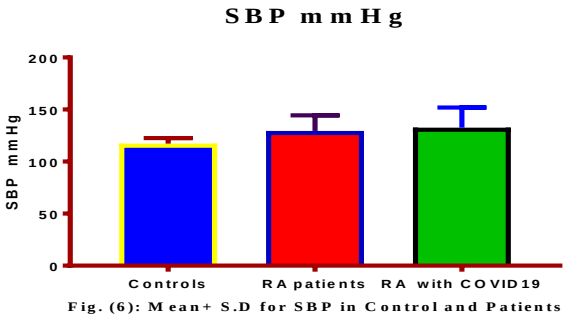

Fig. (6): Mean+ S.D for SBP in Control and Patients

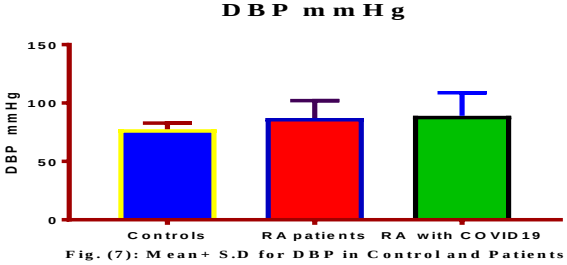

Fig. (7): Mean+ S.D for DBP in Control and Patients

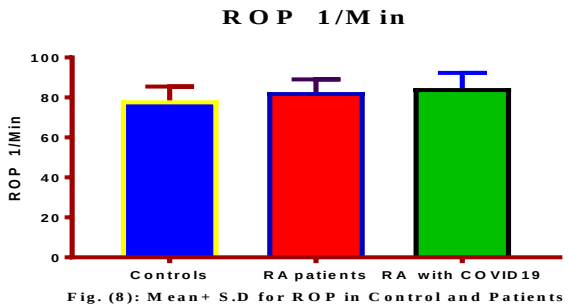

Fig. (8): Mean+ S.D for ROP in Control and Patients

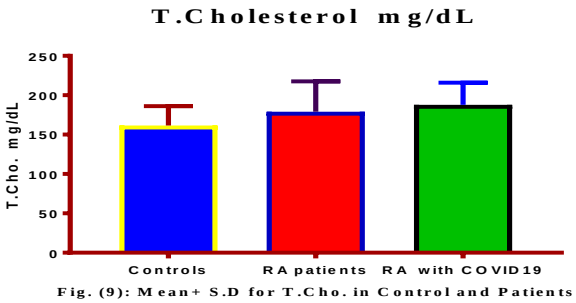

Fig. (9): Mean+ S.D for T.Cho. in Control and Patients

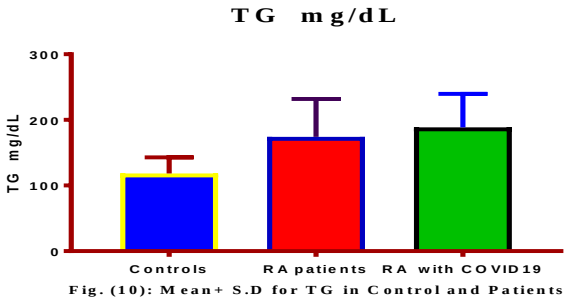

Fig. (10): Mean+ S.D for TG in Control and Patients

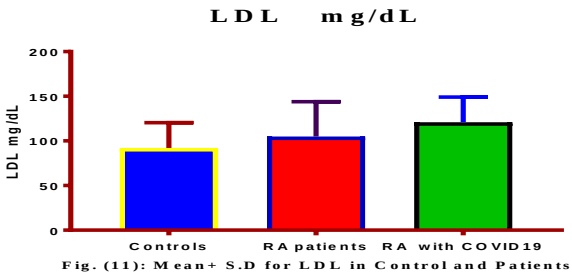

Fig. (11): Mean+ S.D for LDL in Control and Patients

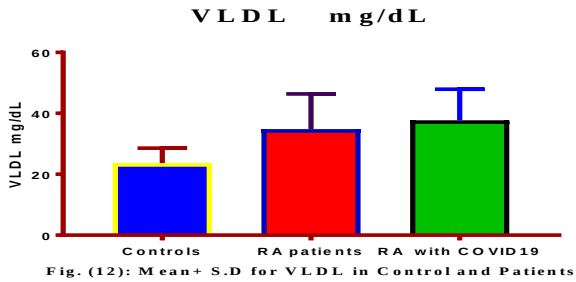

Fig. (12): Mean+ S.D for VLDL in Control and Patients

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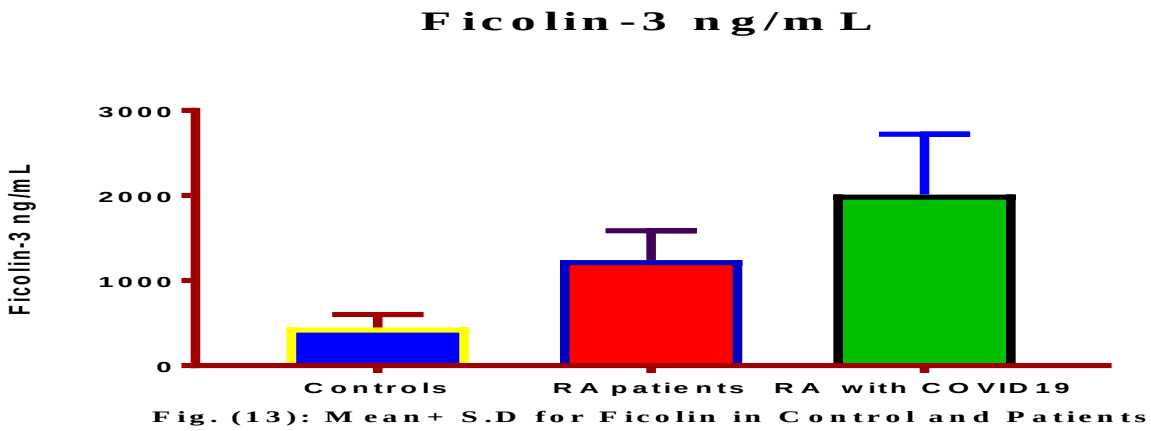

Fig. (13): Mean+ S.D for Ficolin in Control and Patients

As Table 3 shows, the ROC curve established that serum FCN-3 and BMI levels exhibited a good method for discriminating' between healthy individuals, patients with RA and RA with Covid-19 patients [0.9936; p<0.001; 95% conference lnterval (cl); 0.9813 to 1.006 and SE: 0.006308] (Fig. 14), [AUC= 0.926; p<0.0001; 95%confidence interval (cl); 0.8372 to 1.015 and SE: 0.04532] (Fig. 15)
while (SBP, DBP, ROP, T.cholesterol and VLDL) showed a good discriminatory efficacy between healthy individuals, patients withRA and RA with Covid-19 patients [AUC=0.7589 ;P=0.0009 ;95% confidence interval (cl): 0.6289 to 0.889 and SE: 0.06635] (Fig.16), [RUC=0.7098; p=0.0070; 95% confidence interval (cl): 0.572 to 0.8476 and SE: 0.0703] (Fig. 17), [RUC= 0.7022; p=0.0094; 95% confidence interval (cl): 0.5648 to 0.8395 and SE: 0.07007] (Fig. 18), [RUC=0.727; p=0.0035; 95% confidence interval (cl):0.5931 to 0.861 and SE:0.06832] (Fig. 19), [RUC=0.7934; p=0.0002; 95% confidence interval (cl): 0.6623 to 0.9244 and SE: 0.06687] (Fig. 20) While group[AUC value from (0.5-0.7) showed low validity in predicting validity this group includes W/H, W/N, D of RA , HDL and Age [RUC=0.6116; p=0.1516; 95% confidence interval(cl): 0.4631 to 0.7601 and SE: 0.07577] (Fig. 21), [RUC=0.6288; p=0.0979; 95% confidence interval (cl): 0.4816 to 0.7761 and SE:0.07514] (Fig. 22), [RUC= 0.6276; p=0.1013; 95% confidence interval (cl): 0.4803 to 0.7748 and SE: 0.07513] (Fig. 23), [RUC=0.6798; p=0.0209; 95% confidence interval (cl): 0.5361 to 0.8236 and
SE:0.07333] (Fig. 24), [RUC=0.5357; p=0.6464; 95% confidence interval(cl): 0.3822 to 0.6893 and SE: 0.07835] (Fig. 25). As Table 3 shows, the ROC curve established that serum FCN-3 and BMI levels exhibited a good method for discriminating' between healthy individuals, patients with RA and RA with Covid-19 patients [0.9936; p<0.001; 95% conference lnterval (cl); 0.9813 to 1.006 and SE: 0.006308] (Fig. 14), [AUC= 0.926; p<0.0001; 95%confidence interval (cl); 0.8372 to 1.015 and SE: 0.04532] (Fig .15).

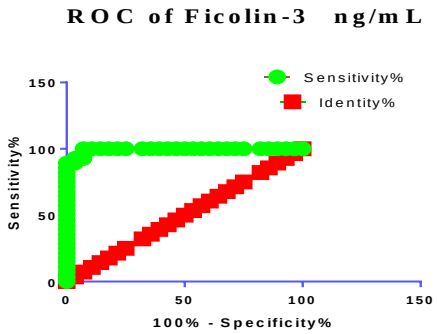

Fig. 14. ROC curve displaying AUC of FCN-3 n RA patients

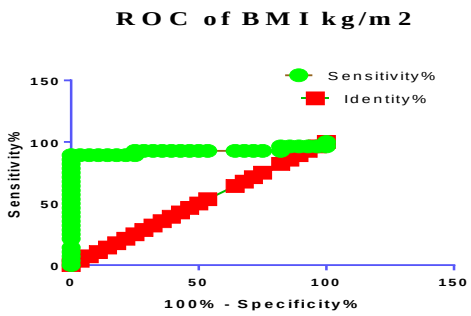

Fig. 15. ROC curve displaying AUC of BMI in RA patients

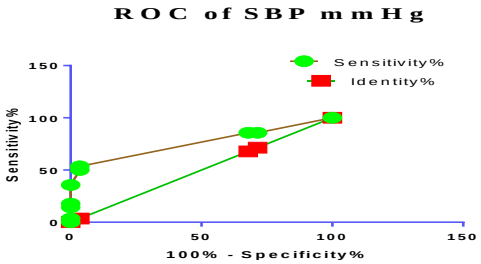

Fig. 16. ROC curve displaying AUC of SBP in RA patients

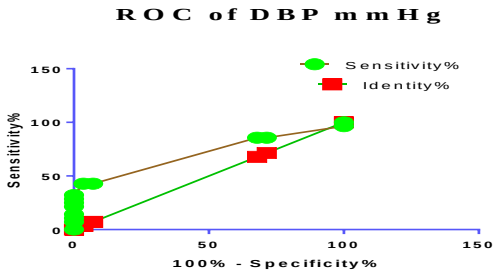

Fig. 17. ROC curve displaying AUC of DBP in RA patients

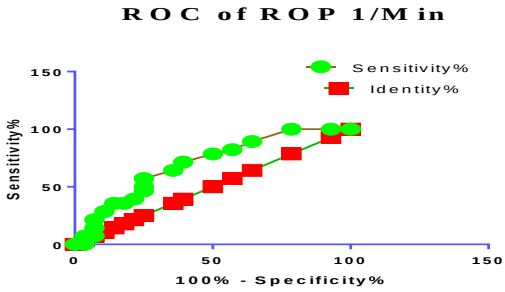

Fig. 18. ROC curve displaying AUC of ROP in RA patients

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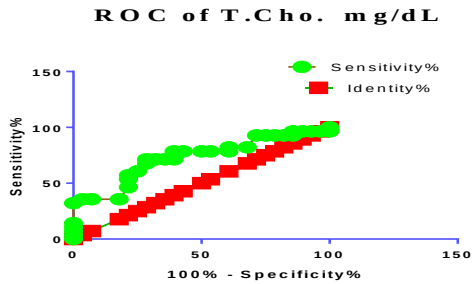

Fig. 19. ROC curve displaying AUC of T.Cho in RA patients

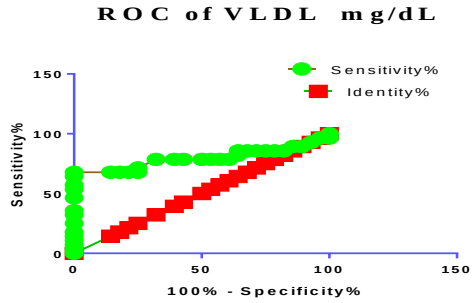

Fig. 20. ROC curve displaying AUC of VLDL in RA patients

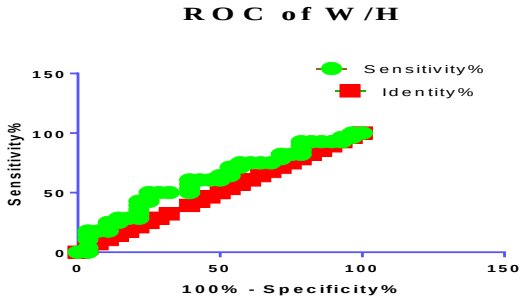

Fig. 21. ROC curve displaying AUC of W/H n RA patients

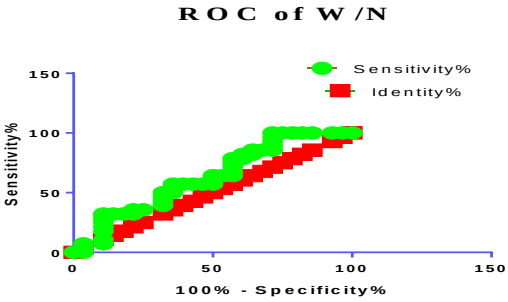

Fig. 22. ROC curve displaying AUC of W/N in RA patients

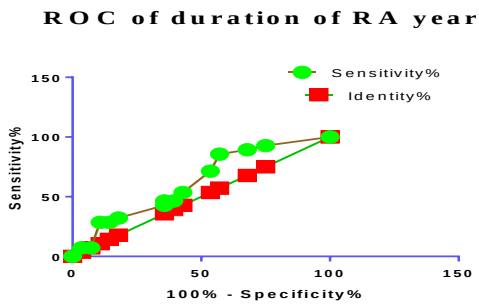

Fig. 23. ROC curve displaying AUC of D of RA in RA patients

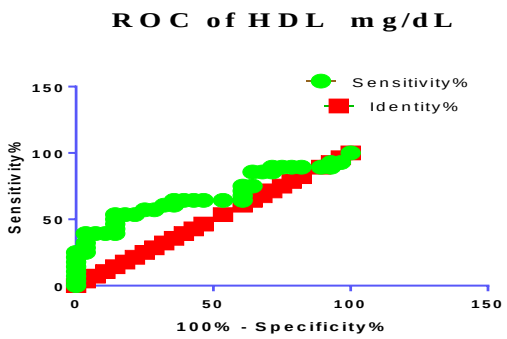

Fig. 24. ROC curve displaying AUC of HDL in RA patients

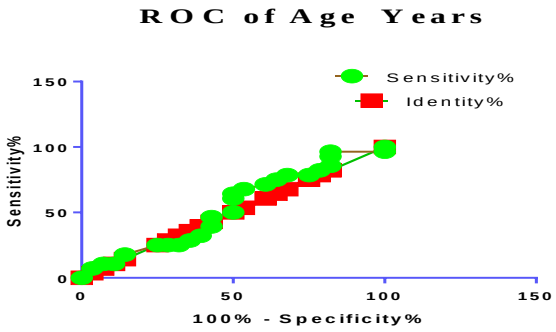

Fig. 25. ROC curve displaying AUC of Age in RA patients

Table 3. Area under the ROC curve for all analyzed Biomarkers

Parameter	AUC	Std. Error	95% confidence interval	P-value
Age Years	0.5357	0.07835	0.3822 to 0.6893	0.6464
BMI kg/m2	0.926	0.04532	0.8372 to 1.015	<0.0001
W/H	0.6116	0.07577	0.4631 to 0.7601	0.1516
W/T	0.5651	0.07761	0.4129 to 0.7172	0.4033
W/N	0.6288	0.07514	0.4816 to 0.7761	0.0979
SBP mmHg	0.7589	0.06635	0.6289 to 0.889	0.0009
DBP mmHg	0.7098	0.0703	0.572 to 0.8476	0.0070
ROP 1/Min	0.7022	0.07007	0.5648 to 0.8395	0.0094
D of RA Years	0.6276	0.07513	0.4803 to 0.7748	0.1013
T.Cho. mg/dL	0.727	0.06832	0.5931 to 0.861	0.0035
TG mg/dL	0.7934	0.06687	0.6623 to 0.9244	0.0002
HDL mg/dL	0.6798	0.07333	0.5361 to 0.8236	0.0209

LDL mg/dL	0.6454	0.07477	0.4989 to 0.792	0.0341
VLDL mg/dL	0.7934	0.06687	0.6623 to 0.9244	0.0002
Ficolin-3 ng/mL	0.9936	0.006308	0.9813 to 1.006	<0.0001

4. DISCUSSION

Rheumatoid arthritis is an autoimmune inflammatory infection involving articular synovial propagation or lacking a general inflammatory response [15]. Ficolins are key proteins of the lectin pathway of complement able to recognize pathogen-associated molecular patterns, apoptotic cells and cellular debris mediating the clearance by phagocytes. High ficolin-1 and ficolin-3 levels have been observed in RA patients [16], The relationship between RA and infectious diseases is very complex. Compared with the general population, RA patients have an increased risk of infection [17]. At the beginning of the COVID-19 outbreak, concerns have arisen about the possible consequences of SARS-CoV-2 infection in patients with RA. Given the potential adverse effects of immunosuppressive drugs on viral clearance, there have been concerns that infection will be associated with increased severity of COVID-19 and excessive mortality in patients with rheumatic COVID-19 in RA patients is to review large numbers of patients and diagnose COVID-19 in terms of limitations of clinical testing [18]. The overall and dose-response meta-analysis showed that increased BMI was associated with an increased risk for rheumatoid arthritis, which might present a prevention strategy for the prevention or control of rheumatoid arthritis. The nonlinear relationship between BMI and RA might present a personal prevention strategy for RA [19].

A study has demonstrated, FCN3 levels were found to be significantly higher in RA patients than in HCs [20], To increase our knowledge concerning the function of ficolin-3 in persons who are at a high risk for developing RA, we tested FCN3 indicator, we established that many high-risk indicators for RA were related to increased concentrations of FCN3, including, obesity-linked factors, ESR, creatinine and TG. in patients with RA than in HCs. Nevertheless, FCN3 concentrations were also clearly related with the AMs like W/H, W/T and W/N, as well as with ESR and SBP, DBP and TG.

The incidence of RA was found to have a link to higher values of Wt., W/H, W/T, W/N, SBP, DBP, ESR, RF, creatinine, urea, UA, TC, TG, BMI and lower HDL content are, all related to worsening and prolonged irritation in ongoing RA illnesses [20]. The outcomes of this study reveal clear differences in the circulation of abdominal fat between RA patients and HCs, with; significant variations in BMI. Greater quantities of visceral fat were closely linked to an increase in a number of cardiometabolic risk factors in RA patients in comparison to HCs. In RA patients a number of inflammatory and noninflammatory mediators may lead to these detected changes, involving certain elements that are adaptable for controlling RA (e.g., regulating accumulative contact to glucocorticoids). Our findings, which show a link between RA and higher W/H, W/T, W/N and BMI, also show that both subcutaneous fatty acids (SFA) and visceral fatty acids (VFA) were related with CV risk factors (SBP, DBP, TC, HDL and TG).; Nevertheless, only visceral fat stayed closely related with risk factors for developing RA, later accounting for further AMs. Therefore, augmented visceral fat may explain the higher risk of CVD detected in RA patients [21].

The initial causes of elevated VFA and SFA in RA patients may be multifactorial. In the current study, we recognized three RA disease reasons relationships associated with augmented VFA in both men and women: W/H, W/T and W/N. The reason for the relationship between these AMs and VFA is not clear. Since there is no identified biological relation among RA and adipose increase, the link may be associated with RF, as a disease severity indicator. Nevertheless, other indicators for the severity of RA that were evaluated in our study (e.g., ESR) showed no relation to VFA.

The outcome of this study presented W/H, W/T, W/N and obesity as risk factors for developing RA., Similarly, these AMs are linearly related with FCN-3. A reasonable hypothesis to explain the increased risk of developing RA in overweight persons is that obesity may stimulate autoimmunity via a range of mechanisms involving the excretion of adipokines [22]. Although, no specific biological mechanism has been identified to account for this positive relationship, the present study supports [23] findings that indicated a positive relationship between increasing BMIs and the development of RA.

The results of the present study give support to the notion that there may be local associations ficolin-3 in certain AMs for patients with RA and patients RA with COVID-19

This study showed that serum levels of FCN-3 are related with quick weakening of RA, according to the most recent research. Our findings support the hypothesis that high FCN-3 levels may be contributing to rising incidence of RA in Iraqi subjects, and may serve as a novel predictor of RA progression in Iraqi patients.

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