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# A relationship of contactin-1 with a number of trace elements in Iraqi rheumatoid arthritis patients with and without COVID-19

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***Abstract*---**Background: Anti-inflammatory intermediaries like contactin-1 (CNTN-1) play an essential role in regulating several diseases, such as Rheumatoid Arthritis (RA). This paper explores the relationship between CNTN-1 and a number of trace elements in RA patients with and without COVID19. Accordingly, it investigates whether there are any correlations between CNTN-1 and some trace elements. Materials and Methods: The paper involved 56 patients, where 28 suffer from RA without any complications, the other 28 have RA with COVID19 attending Al-Fallujah teaching hospital and 28 healthy persons matching in age, sex and ethnic background as control group. Serum level of contactin-1 was estimated by ELISA technique while Uric acid, urea, creatinine, lipid Profile, zinc, copper, ferrous and magnesium were assessed by colorimetric enzymatic methods. Results: The results demonstrated that Contactin-1 serum concentrations had existed more significantly in patients with and without COVID19. However, RA patients and RA with Covid-19 patients showed lower levels of magnesium (Mg), zinc (Zn), iron (Fe) and Fe/Cu ratio. High serum concentrations of CNTN-1 have been identified and associated positively with ESR and Cu/Zn, while serum concentrations of CNTC-1 were positively related with total cholesterol (TC), triglycerides (TG), copper (Cu), zn and iron (Fe). Compared to other biomarkers studies, ESR and CNTN-1 showed the highest ROC curve value. Conclusion: Serum CNTN-1 levels can be used as a novel biomarker in the detection of RA and may be an effective biomarker in the diagnostic of RA with and without COVID19.

***Keywords*---**CNTN-1, rheumatoid Arthritis, COVID-19, trace elements.

**Introduction**

As a systemic autoimmune disease, Rheumatoid Arthritis (RA) has inflammatory Arthritis and extra-articular involvement characteristics. of unknown etiology, it is a chronic inflammatory disease and exists the synovial joints essentially. In small peripheral joints, the RA begins. It is usually symmetrical. If it is untreated, it progresses to include nearby joints. With the erosion of cartilage and bone, Arthritis, over time, leads to joint destruction [1].

The coronavirus family has both animal and human pathogens. In Wuhan, Huanan, a new coronavirus was found, at the end of 2019, due to pneumonia cases cluster of no etiology causes. The primary location for cases of Coronavirus disease 2019 (COVID-19) is Seafood wholesale market in a city in China's Hubei Province. The new Corona virus spread quickly, which led to its spread. In a pandemic across China, followed by a blood epidemic and a rapid worldwide increase in the number of cases [2]. Which prompted the World Health Organization (WHO) declares a public health emergency in late January 2020, describing it as a pandemic in March 2020, appointed by the World Health Organization Disease like Coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the nomination of the virus that causes Coronavirus. It is then known as a novel coronavirus (2019-nCoV) [3].

Contactin-1 is a 130 kDa protein, which is present in a membrane-bound and soluble form [4]. With an extracellular domain, neural cell adhesion/recognition molecules' prototype consists of 6 aminoterminal immunoglobulin-like and 4 fibronectin-like structural domains. Through a glycosyl phosphatidyl inositol (GPI) moiety, they are attached to the plasma membrane [5]. A recent study in patients showed that contactin-1 is significantly higher than that of controls [6].

Trace elements are widely distributed in a variable proportion in human body and they play a vital role in growth. Zinc forms a part of each cell in a body. Additionally, it is a part of three-hundred enzymes. These enzymes' functions vary from cell growth to the appropriate action of the hormones of the body. Growth retardation can be caused by zinc deficiency [7]. It is essential for maintaining a proper immune response [8]. Copper is important in key metalloenzymes such as monamine oxidase, tyrosinase, oxidase, cytochrome, and ceruluplasmine [9]. In addition ceruloplasmin, it used in many enzymes as it is essential in the work of enzyme superoxide dismutase (SOD). Furthermore, it is important in the oxidation enzyme Lysyl oxidase work. This enzyme is necessary for connective tissue synthesis. It has been stated that lacking of the oxidation enzyme Lysyl oxidase causes decreasing in copper, which may harm connective tissue and bones [10]. Free radical production and damage can be caused by increases in copper with iron. In poor collagen integrity, copper deficiency also leads to blood vessel rupture [11].

Magnesium is a part of several biochemical reactions in the bone, where it involves in the processes of more than three hundred enzymatic processes. To form new calcium crystals, magnesium activates the enzyme alkaline phosphatase. Furthermore, magnesium is required for vitamin D conversion to its biologically active form of 1,25 dihydroxy vitamin D3. The syndrome of vitamin D

resistance can be produced by magnesium deficiency. In comparison with the concentration of extracellular magnesium, there is a high intracellular magnesium concentration. Accordingly, it attributes the increase in the concentration of output cells to cell damage. It then leads to an increase in blood serum concentration [12]. Therefore, in the structure of bones, magnesium is essential. Reduction in magnesium leads to tetany and may result in calcium reduction. Therefore, magnesium is important to the healthy functioning of muscles and nerves as it maintains acid-base balance in the body [13]. Iron transports oxygen to it cells and is necessary to produce energy [14]. It exists in both types Iron and steel. Compared to ferrous iron, iron in iron form is better absorbed. Iron reduction anemia in many persons leads to death from infection due to a weak immune system. In maintaining immunity, iron covers all parts of how the system works [15]. There is a possibility that iron impacts oxidative injury mediated by diseases such as RA [16]. Finally, it is important to mention that as ferritin hemosiderin, a large amount of iron is stored.

Previous study in 2017, displayed Fe levels and serum Zn in patients with RA considerably lower than in healthy controls. However, in RA patients, the levels of Cu were determined to be higher. Additionally, in RA patients, there was a negative association between Cu and Zn. Nevertheless, the control group didn't show any correlation, according to trace element correlation analyses. In RA patients, it is critical to investigate the deficit of crucial trace metals in biological samples from various demographics, as this information may be useful in the diagnosis and treatment of rheumatoid arthritis patients [17].

The central goal of this paper to evaluate contactin-1 serum levels in RA patients without and with COVID19 and to determine the correlation of cotactin-1 with some trace elements in RA patients without and with COVID19.

**Methods**

The participated in the study included 56 patients, 28 patients with RA and of whom infected with COVID-19 previously diagnosed with RA who were coming to the rheumatology unit-the Al- Fallujah teaching hospital and Al-Shifaa hospital (Anbar, Iraq). This study performed from November 2021 to February 2022. The American rheumatism association's 1987 revised principles for RA classification were used to diagnose the patients [18]. For the purpose of comparison, 28 persons were choosing as controls group, with no history of any rheumatic, the age ranges from 35 to 65 years. Demographic data and anthropometric measurements (AMs) of patients with HCs and RA were determined. By a stadiometer, the anticipation of height was 0.01 m sans shoes and socks.

Additionally, the weight estimation was near large clothing, extra accessories, socks and 0.1 kg shoes. The division of weight (kg) section of height (m) calculates the BMI (kg/m2). With a Thermo Scientific Varioskan microplate reader system, an ELISA kit (BT LAB Inc, China) has been used to determine the concentration of CNTN-1 in the subject. Finally, in this work, the rest biochemical parameters were calculated using available commercial kits through coloured enzymatic method.

**Statistical Analysis**

GraphPad prism v.8 and SPSS v.24 were utilized to conduct the analyses. The level of statistical importance has been at P<0.05. The mean and standard deviation (SD) (descriptive statistics) were determined for every parameter. The one-way ANOVA test has been used to compare RA groups and HCs. Pearson's correlation (r=−1 to 1) was used to study the associations between parameters and the CNTN-1. To evaluate the best biomarker, we created the curve of a receiver operating characteristic (ROC). The best biomarker may be used to diagnose RA patients with and without COVID19.

**Results**

As illustrated in **Figure 1** and **Table 1**, Data of this study showed, the mean of ESR (mm/H) was higher among RA patients with Covid-19, RA Patients without COVID-19 and HCs (75.66 ± 14.9), (48.43 ± 14.55) and (12.46 ± 2.978) respectively, (P< 0.0001), the mean urea (mg/dL) was higher among RA patients with Covid-19, RA Patients and HCs were (54.64 ± 14.46), (22.61 ± 8.871) and (19.88 ± 5.783) respectively. Urea has shown significant differences (P< 0.0001), **(**see **Figure 2** and **Table 1)**, the mean creatinine, uric acid (mg/dL), Mg (mEq/L) and Zn/Fe showed non-significant difference in RA patients with Covid- 19, RA patients and HCs were (P=0.0026), (P=0.0218), (P=0.0579) and (P=0.1376) respectively, as shown in **(Table 1, Fig 3 → 6 respectively)**,

The results demonstrated that the mean Cu, Zn, Fe (mg/dL), Cu/Zn and Fe/Cu of RA patients with Covid- 19, RA patients and HCs were (100.4 ± 19.46), (90.28 ± 18.02), (75.77 ± 17.06) and (65.53 ± 20.42), (77.45 ± 17.13), (91.41 ± 15.54) and (64.16 ± 18.58), (89.02 ± 20.31), (104.2 ±19.62) respectively, as shown in **(Table 1, Fig 7 → 11 respectively)**.

Lastly, as illustrated in **Figures 1** and **2,** and **Table 1**, this work proved that RA patients with Covid-19 and RF patients have significantly higher level of CNTN-1 (ng/mL) than those found in HCs (P<0·001). (42.07±12.72), (32.77± 11.57) and (11.74 ± 4.356).

**Table 2** shows the correlations of CNTN-1 with the parameters of both groups (control and patients). The table demonstrates a great association between CNTN-1 and ESR, urea, creatinine, uric acid, Mg, Cu, Fe, and Cu/Zn (p=<0.01; r=0.733), (p=<0.01; r=0.499), (p=0.018, r=0.261), (p=0.167; r=0.152), (r=-0.200; p=0.068), (p=<0.01; r=0.469), (p=<0.01; r=-0.477), (p=<0.01; r=-0.623); (p=<0.01; r=0.525), respectively.

Table 1. Mean and S.D of studied biomarkers of Controls and RA patients with and without COVID19

| Parameter | Controls | | RA Patients | | RA with Covid19 | | p-value |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | |
| ESR (mm/H) | 12.46 | 2.978 | 48.43 | 14.55 | 75.66 | 14.9 | <0.0001 |
| Urea (mg/dL) | 19.88 | 5.783 | 22.61 | 8.871 | 54.64 | 14.46 | <0.0001 |
| Creatinine (mg/dL) | 0.5537 | 0.1558 | 0.6311 | 0.1846 | 0.74 | 0.2292 | 0.0026 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Uric acid (mg/dL) | 3.996 | 1.557 | 4.832 | 1.611 | 5.009 | 1.047 | 0.0218 |
| Mg (mEq/L) | 2.194 | 0.3344 | 2.026 | 0.3093 | 2.007 | 0.3058 | 0.0579 |
| Cu (mg/dL) | 75.77 | 17.06 | 90.28 | 18.02 | 100.4 | 19.46 | <0.0001 |
| Zn (mg/dL) | 91.41 | 15.54 | 77.45 | 17.13 | 65.53 | 20.42 | <0.0001 |
| Fe (mg/dL) | 104.2 | 19.62 | 89.02 | 20.31 | 64.16 | 18.58 | <0.0001 |
| Cu/Zn | 0.8433 | 0.2117 | 1.233 | 0.4172 | 1.721 | 0.7607 | <0.0001 |
| Fe/Cu | 1.478 | 0.5543 | 1.035 | 0.3414 | 0.6544 | 0.1997 | <0.0001 |
| Zn/Fe | 0.9198 | 0.2746 | 0.9229 | 0.3277 | 1.092 | 0.4656 | 0.1376 |
| Contactin-1 (ng/mL) | 11.74 | 4.356 | 32.77 | 11.57 | 42.07 | 12.72 | <0.0001 |
| D-Dimer (ng/mL) | ------- | ------- | ------- | ------- | 2042 | 678.7 | ------- |
| Ferritin (ng/mL) | ------- | ------- | ------- | ------- | 815.7 | 254.3 | ------- |

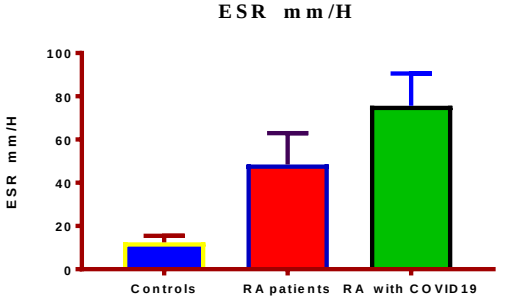



Fig. (1): Mean+ S.D for ESR in Control and Patients

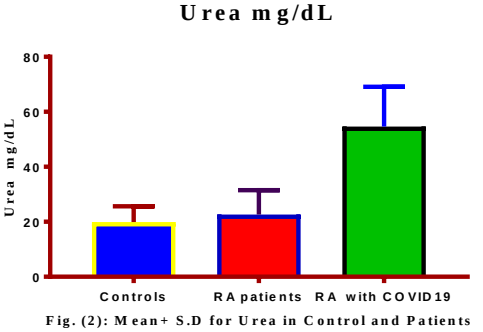



Fig. (2): Mean+ S.D for Urea in Control and Patients

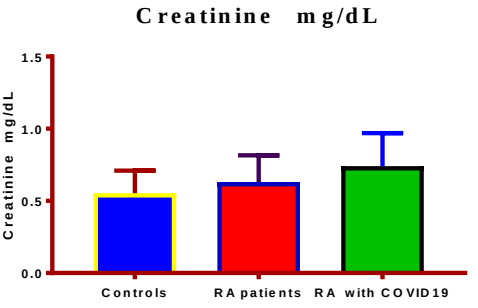



Fig. (3): Mean+ S.D for creatinine in Control and Patients

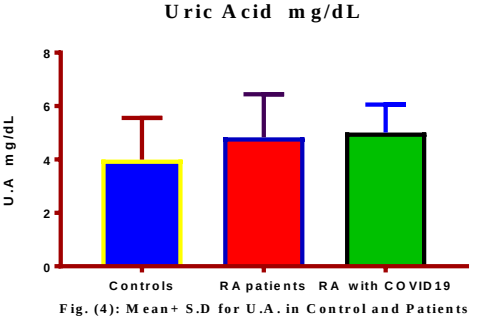



Fig. (4): Mean+ S.D for U.A. in Control and Patients

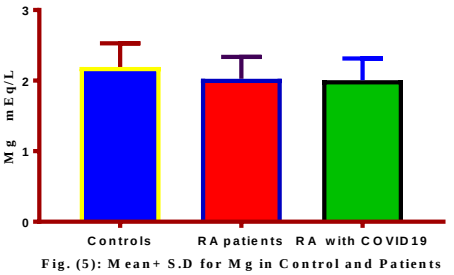



Fig. (5): Mean+ S.D for Mg in Control and Patients

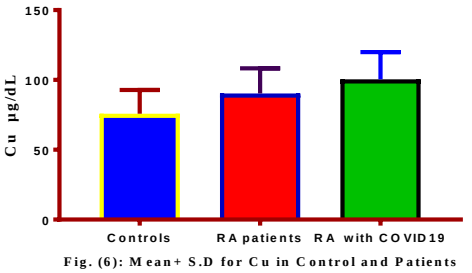



Fig. (6): Mean+ S.D for Cu in Control and Patients

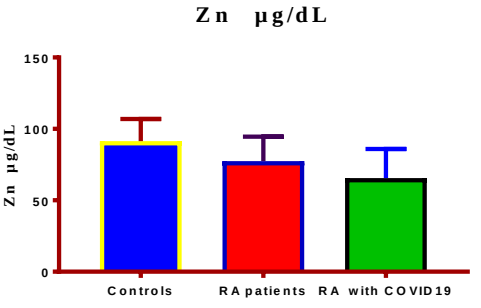



Fig. (7): Mean+ S.D for Zn in Control and Patients

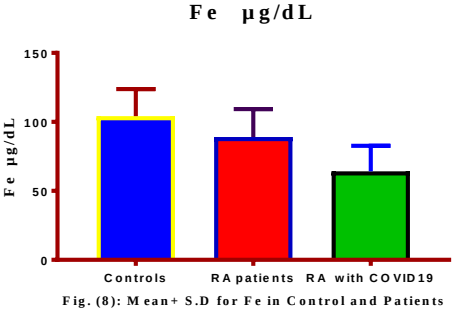



Fig. (8): Mean+ S.D for Fe in Control and Patients

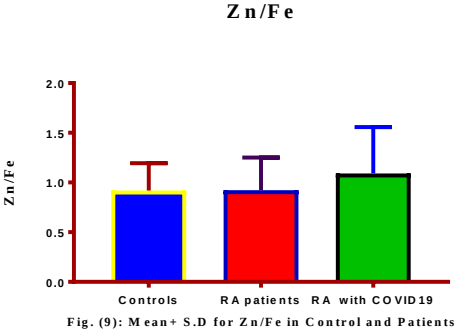



Fig. (9): Mean+ S.D for Zn/Fe in Control and Patients

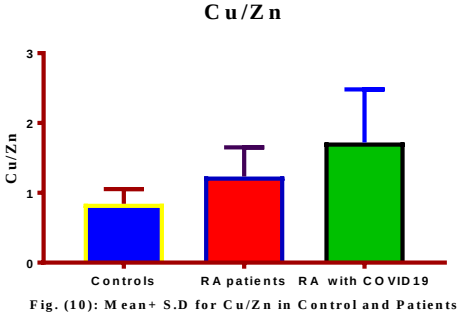



Fig. (10): Mean+ S.D for Cu/Zn in Control and Patients

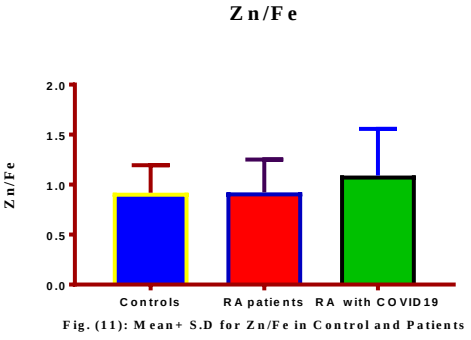



Fig. (11): Mean+ S.D for Zn/Fe in Control and Patients

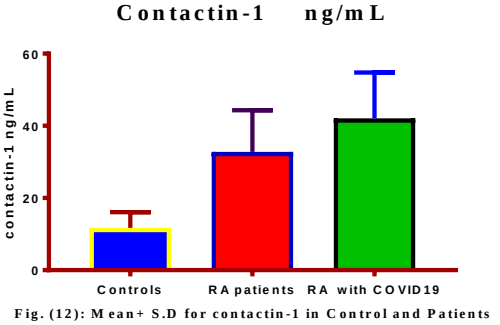



Fig. (12): Mean+ S.D for contactin-1 in Control and Patients

Table 2. Correlation of Contactin-1 with other parameters in the study

| Parameter | | Contactin-1 ng/mL (r ) | p-value |
|---|---|---|---|
| ESR | (mm/H) | 0.733 | <0.01 |
| Urea | (mg/dL) | 0.499 | <0.01 |
| Creatinine | (mg/dL) | 0.261 | 0.018 |
| Uric acid | (mg/dL) | 0.152 | 0.167 |
| Mg | (mEq/L) | -0.200 | 0.068 |
| Cu | (mg/dL) | 0.469 | <0.01 |
| Zn | (mg/dL) | -0.477 | <0.01 |
| Fe | (mg/dL) | -0.623 | <0.01 |
| Cu/Zn | | 0 525 | <0.01 |
| Fe/Cu | | -0.622 | <0.01 |
| Zn/Fe | | 0.178 | 0.104 |

Area under ROC curve established that serum CNTN-1, ESR and levels of Cu/Zn showed a good method for distinguishing between patients with RA, RA with Covid-19 patients, healthy persons [AUC= 0.9643; p<0.001; 95% conference lnterval (cl); 0.9241 to 1.004 and SE: 0.0205], [AUC= 1; p<0.0001; 95% confidence interval (cl); 1 to 1and SE: 0] and [AUC= 0.8329; p<0.0001; 95%confidence interval (cl); 0.7269 to 0.9389 and SE: 0.05407] **Table 3 (Figures 13→ 15 respectively)**, while (T.Cho, TG, VLDL, Cu, Zn, Fe and Fe/Cu) showed an accepted distinguishing efficiency between patients withRA and RA with Covid-19 patients and healthy individuals [AUC=0.727 ;P=0.0035 ;cl = 95%: 0.5931 to 0.861 and SE: 0.06832], [RUC=0.7934; p=0.0002; cl = 95%: 0.6623 to 0.9244 and

SE: 0.06687], [RUC= 0.7934; p=0.0002; cl = 95%: 0.6623 to 0.9244 and SE: 0.06687], [RUC=0.7232; p=0.0041; cl = 95%:0.5913 to 0.8552 and SE:0.06733], [RUC=0.7258; p=0.0037; cl = 95%: 0.5918 to 0.8597 and SE: 0.06834], [RUC=0.7194; p=0.0048; cl = 95%: 0.584 to 0.8548 and SE: 0.06909] and [RUC=0.7462; p=0.0016; cl = 95%: 0.6172 to 0.8751 and SE: 0.06579] **Table 3 (Figures16 → 22 respectively)**,

While group [AUC value from (0.5-0.7) showed low validity in predicting validity this group includes urea, creatinine, uric acid, HDL, LDL, Mg and Zn/Fe [RUC=0.6276; p=0.1013; 95% confidence interval (cl): 0.4758 to 0.7793 and SE: 0.07741], [RUC=0.6124; p=0.01524; 95% confidence interval (cl): 0.4621 to 0.7628 and SE: 0.0767], [RUC= 0.6429; p=0.0665; 95% confidence interval (cl): 0.4981 to 0.7876 and SE: 0.07384], [RUC=0.6798; p=0.0209; 95% confidence interval (cl): 0.5361 to 0.8236 and SE:0.07333], [RUC=0.6454; p=0.341; 95% confidence interval (cl): 0.4989 to 0.792 and SE: 0.07477]**.** [RUC=0.6307; p=0.0930; 95% confidence interval (cl): 0.4851 to 0.7764 and SE: 0.07433]**,** [RUC=0.5026; p=0.9739; 95% confidence interval (cl): 0.3488 to 0.6563 and SE: 0.07843] **Table 3 (Figures 23 → 29 respectively)**,

Table 3. The calculated area under the curve of ROC of the Biomarkers

| Parameter | | AUC | Standard Error | 95% cl | P value |
|---|---|---|---|---|---|
| ESR | mm/H | 1 | 0 | 1 - 1 | <0.0001 |
| Urea | mg/dL | 0.6276 | 0.07741 | 0.4758 - 0.7793 | 0.1013 |
| Creatinine | mg/dL | 0.6124 | 0.0767 | 0.4621 - 0.7628 | 0.1524 |
| Uric acid | mg/dL | 0.6429 | 0.07384 | 0.4981 - 0.7876 | 0.0665 |
| T.Cho. | mg/dL | 0.727 | 0.06832 | 0.5931 - 0.861 | 0.0035 |
| TG | mg/dL | 0.7934 | 0.06687 | 0.6623 - 0.9244 | 0.0002 |
| HDL | mg/dL | 0.6798 | 0.07333 | 0.5361 - 0.8236 | 0.0209 |
| LDL | mg/dL | 0.6454 | 0.07477 | 0.4989 - 0.792 | 0.0341 |
| VLDL | mg/dL | 0.7934 | 0.06687 | 0.6623 - 0.9244 | 0.0002 |
| Mg | mEq/L | 0.6307 | 0.07433 | 0.4851 - 0.7764 | 0.0930 |
| Cu | µg/dL | 0.7232 | 0.06733 | 0.5913 - 0.8552 | 0.0041 |
| Zn | µg/dL | 0.7258 | 0.06834 | 0.5918 - 0.8597 | 0.0037 |
| Fe | µg/dL | 0.7194 | 0.06909 | 0.584 - 0.8548 | 0.0048 |
| Cu/Zn | | 0.8329 | 0.05407 | 0.7269 - 0.9389 | <0.0001 |
| Fe/Cu | | 0.7462 | 0.06579 | 0.6172 - 0.8751 | 0.0016 |
| Zn/Fe | | 0.5026 | 0.07843 | 0.3488 - 0.6563 | 0.9739 |
| contactin-1 | ng/mL | 0.9643 | 0.0205 | 0.9241 - 1.004 | <0.0001 |

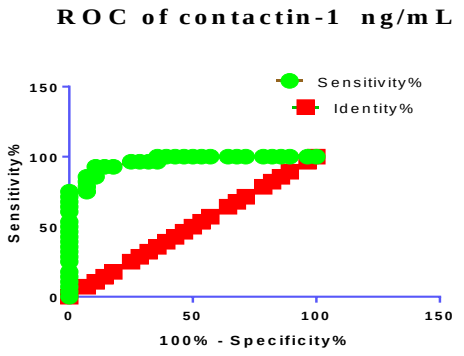



Fig. 13. The curve of ROC presenting AUC of CNTN-1 n RA patients

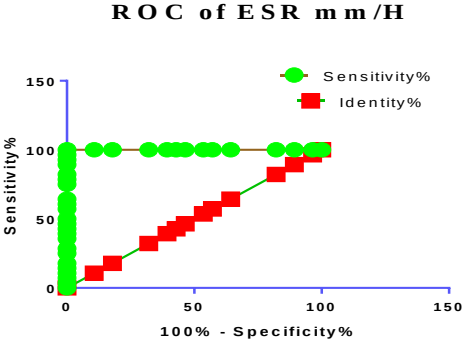
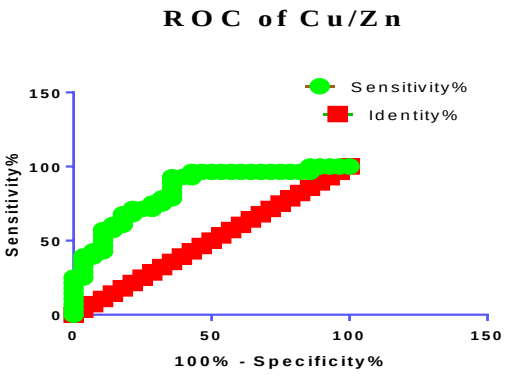



Fig. 14. The curve of ROC presenting AUC of ESR in RA patients



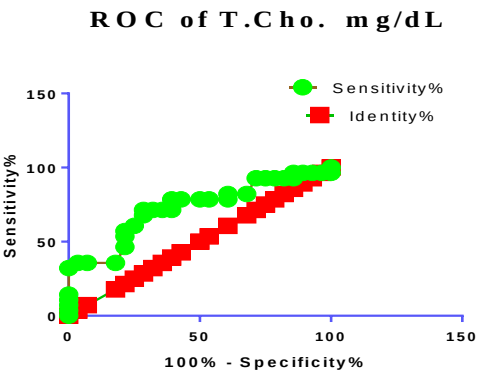
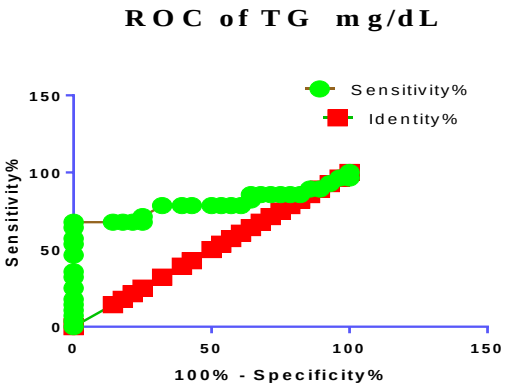




Fig. 15. The curve of ROC presenting AUC of Cu/Zn in RA patients
Fig. 16. The curve of ROC presenting AUC of T.Cho in RA patients



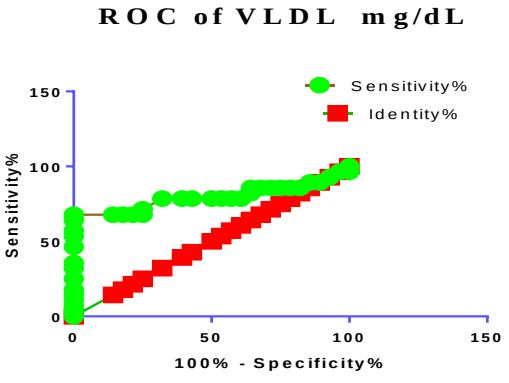
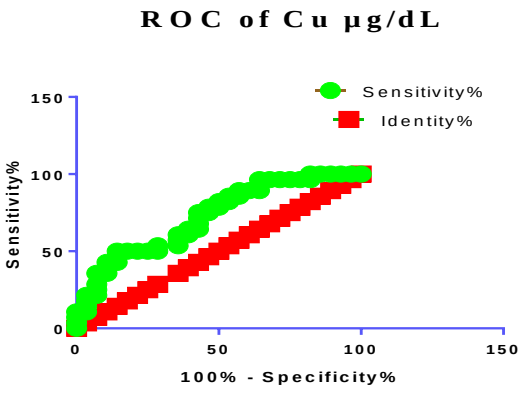




Fig. 17. The curve of ROC presenting AUC of TG in RA patients.
Fig. 18. The curve of ROC presenting AUC of VLDL in RA patients



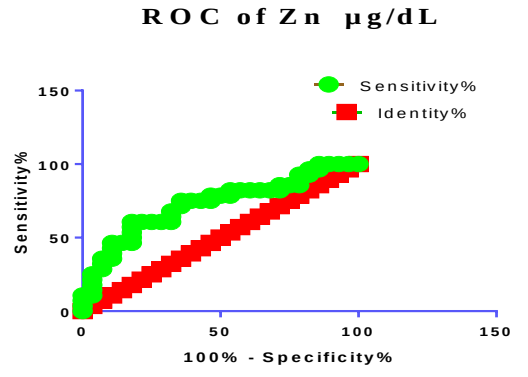
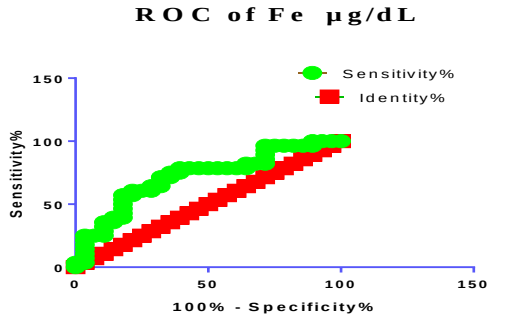




Fig. 19. The curve of ROC presenting AUC of Cu in RA patients
Fig. 20. The curve of ROC presenting AUC of Zn in RA patients



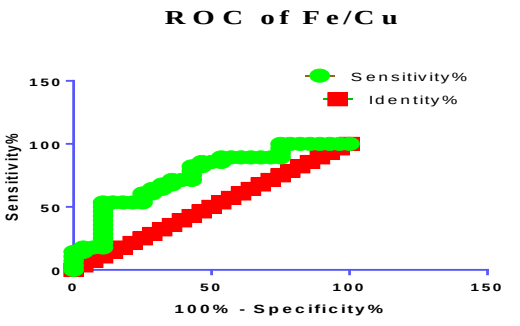
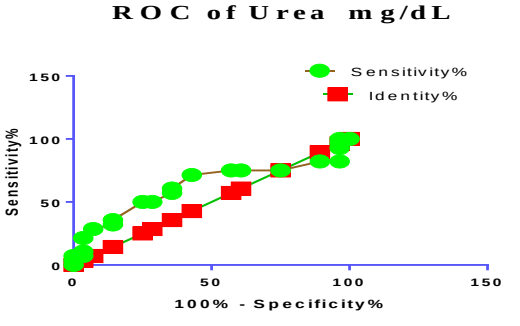




Fig. 21. The curve of ROC presenting AUC of Fe in RA patients
Fig. 22. The curve of ROC presenting AUC of Fe/Cu in RA patients



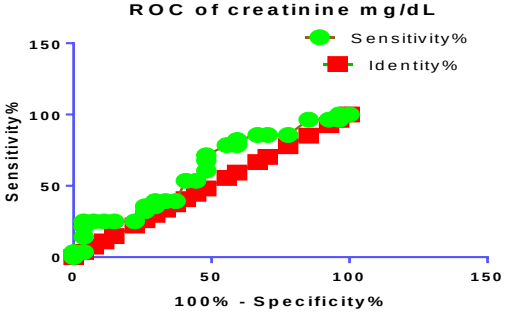
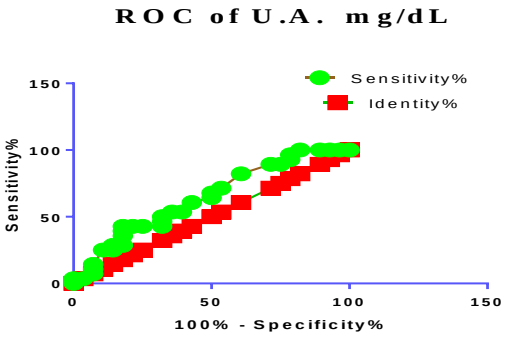




Fig. 23. The curve of ROC presenting AUC of Urea in RA patients.
Fig. 24. The curve of ROC presenting AUC of Creatinine in RA patients



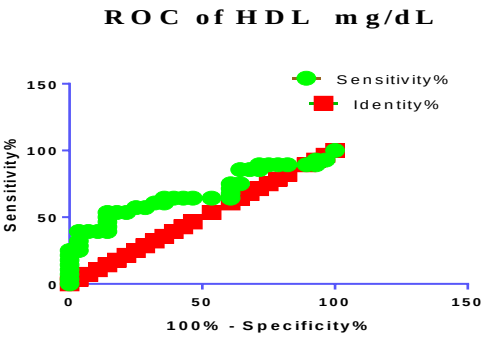




Fig. 25. The curve of ROC presenting AUC of Uric acid in RA patients.
Fig. 26. The curve of ROC presenting AUC of HDL in RA patients

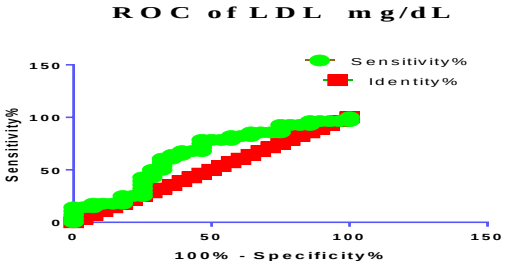



**Fig. 27. The curve of ROC presenting AUC of LDL in RA patients**

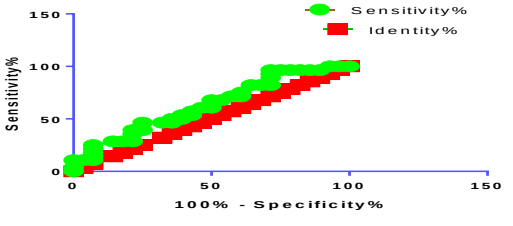



**Fig. 28. The curve of ROC presenting AUC of Mg in RA patients**

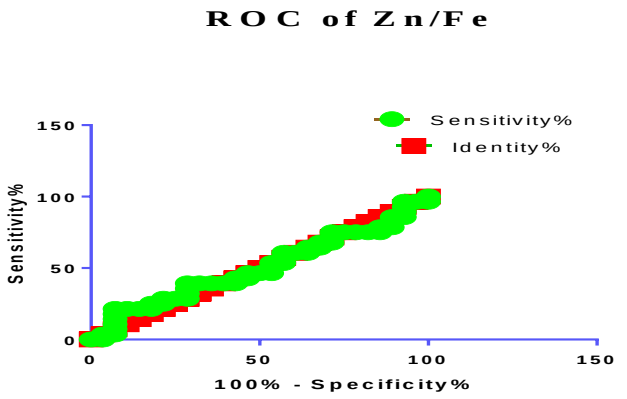



Fig. 29. The curve of ROC presenting AUC of Zn/Fe in RA patients

**Discussion**

As an autoimmune inflammatory disease, Rheumatoid Arthritis lacks a general inflammatory response or articular synovial propagation [19]. CNTN-1 is glycosylphosphatidyl inositol (GPI) anchored membrane protein with six immunoglobulin (Ig)-like domains and four fibronectin type III-like domains. The interactions of Heterophilic between CNTN-1 and its different ligands are crucial in developmental events, such as fasciculation, axonal elongation, neurite growth, myelination, and neural cell adhesion [20].

Recently, CNTN-1 levels have been proven to be greater in patients than in HCs [21]. When COVID-19 started to spread, there were concerns about the possibility of SARS-CoV-2 affecting RA patients. On viral clearance, the concerns led to that immunosuppressive medications may have harmful side effects. Additionally, it was thought that the disease might associate with increasing COVID-19 severity and increase the death rates rapidly in rheumatic COVID-19 patients in RA patients to check and diagnose a lot of COVID-19 patients according to clinical testing limitations [22]. The incidence of RA was found to be associated with higher values of creatinine, TG, TC, UA, and urea. Furthermore, it has lower HDL content, all of which are associated with long-term exacerbation and exacerbation in persistent RA diseases [19]. Most enzymes require trace elements as co-factors and their absence has been linked to a myriad of adverse health effects in humans. The inflammatory response in RA could play a function in trace element metabolism homeostasis. Previous study has displayed serum Zn and Fe levels in RA patients considerably lower than in healthy controls, but Cu levels were identified to be higher in RA patients. There was a negative association between Zn and Cu in the RA patients. However, no correlation has been found in the control group, according to trace element correlation analyses. It is critical to investigate the deficit of crucial trace metals in biological samples of RA patients from various demographics, as this information may be useful in the diagnosis and treatment of rheumatoid arthritis patients [23], as well as decreased levels of Mg.

Similarly, a new study detected the relationship between RA and dietary magnesium in females. To increase the protective role of females with RA, the study demonstrated moderate dietary magnesium intake [24]. The RA incidence was detected to relate to the ESR higher values, creatinine, urea, and uric acid, all related to prolonged and worsening irritation in ongoing RA disease [25]. The finding of this work supported that there are local associations' contactin-1 in certain AMs for patients with RA and patients RA with COVID-19

To conclude, this work demonstrated that patients with RA have high serum contactin-1 levels. It might be the reason for their different complications during the disease course, and it can be utilized as potential biomarkers and predictors of RA, as well as they can be used in the manufacture of new therapies for RA infection.

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