

ORIGINAL ARTICLE

THE RELATIONSHIP BETWEEN ESR AND C-REACTIVE PROTEIN WITH VARIABLE LEVEL OF D-DIMER IN COVID-19

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ABSTRACT

The aim: To show the relationship between these inflammatory factors (ESR, CRP) and D-Dimer level in COVID-19.

Material and methods: This study was started in Al-Mawani teaching hospital in which 74 patient from both genders was included, from August to October 2020. Demographic data, inflammatory marker were taken as the same day of admission to the hospital.

Results: D-Dimer show a moderate positive correlation with ESR, CRP ($r = 0.354$, $p = 0.002$; $r = 0.457$, $p = <0.05$, respectively), while demographical data show no significant relationship.

Conclusion: In SARS-CoV-2 infection, ESR and CRP levels are moderately positively correlated with D-Dimer, and their increasing levels can be used to predict the synchronized rose of D-Dimer after exclusion the possibility of another inflammatory process that may confound the results.

KEY WORDS: COVID-19, ESR, CRP, D-Dimer

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INTRODUCTION

COVID-19 health crises were reported in China, December 2019 by discovering unordinary cases of pneumonia. The disease is caused by RN Virus called Corona that is genetically belongs to the SARS virus group that was identified as (SARS-CoV-2). The WHO declares these cases of severe pneumonia as a pandemic disease that was happened in Wuhan-China [1]. The milestone of this disease was discovered first in 2002 and at that time it was known as SARS-CoV, and in 2012 appeared in Saudi Arabia and was addressed as Middle East Respiratory Syndrome (MERS-CoV) [2]. It was a dilemma health issue which needs for sophisticated investigation like real time polymerase chain reaction swab confirmed by chest CT and blood biochemistry tests (CRP, ferritin, LDH and D-Dimer) with estimation of the level of antibodies by ELISA [3]. C-reactive protein is an inflammatory protein that was discovered as a marker in 1930s, it is synthesized in the liver by the cytokines mainly IL-6 and tissue destruction [4]. High serum level of CRP can be caused by different conditions like bacterial infections, severe tissue damage, different heart problems and few cases of autoimmune and degenerative diseases. It's not necessarily an indicator of a pro-inflammatory event but as a prognostic factor as well [4]. There is a serological test that classifies CRP into classical and high sensitive, standard one can measure high readings which is above 10 mg-l while high sensitive CRP is specified to discover small values in the blood that release from vital organ like brain, heart and its important method recognize the early stage of injury [5]. CRP levels are not related with age, gender, and exercise [5]. CRP can binds to Phosphocholine receptors on the surface of the dead or damaged cells which leads to the activation of complement system and on Fcγ RII expressed on phagocytic cells which leads to the activation of phagocytosis [6]. The erythrocyte sedimentation rate (ESR) is the time required for RBCs to sediment down in the bottom of column of capillary tube per hour [7]. Abundant of fibrinogen in inflammatory condition are released making the RBC in colonies and stick to each other which is presented as high level of ESR because of the increase viscosity of blood that is seen in conditions like renal disease, pregnancy, in female due to menstrual cycle, geriatric, degenerative disease and some types of cancer [8]. ESR is a non-specific indicator of inflammation but it's used as a routine lab test in clinical practice for confirmation of other conditions [9]. ESR levels between 0 to 22 per hour in male and 0 to 29 mm per hour in female is considered to be normal [10]. D-Dimers is a fragment of proteins that released to the circulation after lysis of blood clot when fibrin is catabolized by plasmin. It's one of the diagnostic tools in thrombosis. Therefore any condition that increase the breakdown of fibrin is presented as high serum level of D-Dimer, including COVID-19, venous thrombosis, pulmonary embolism, inflammation, pregnancy, liver disease, surgery, strenuous exercise, trauma and sepsis [11]. Normal D-Dimer is less than 0.5 [12]. In COVID-19 the cytokines plays an important roles in activation of coagulation cascade and deposition of fibrin with damage of vascular endothelium due to hyper inflammatory condition which is commonly seen

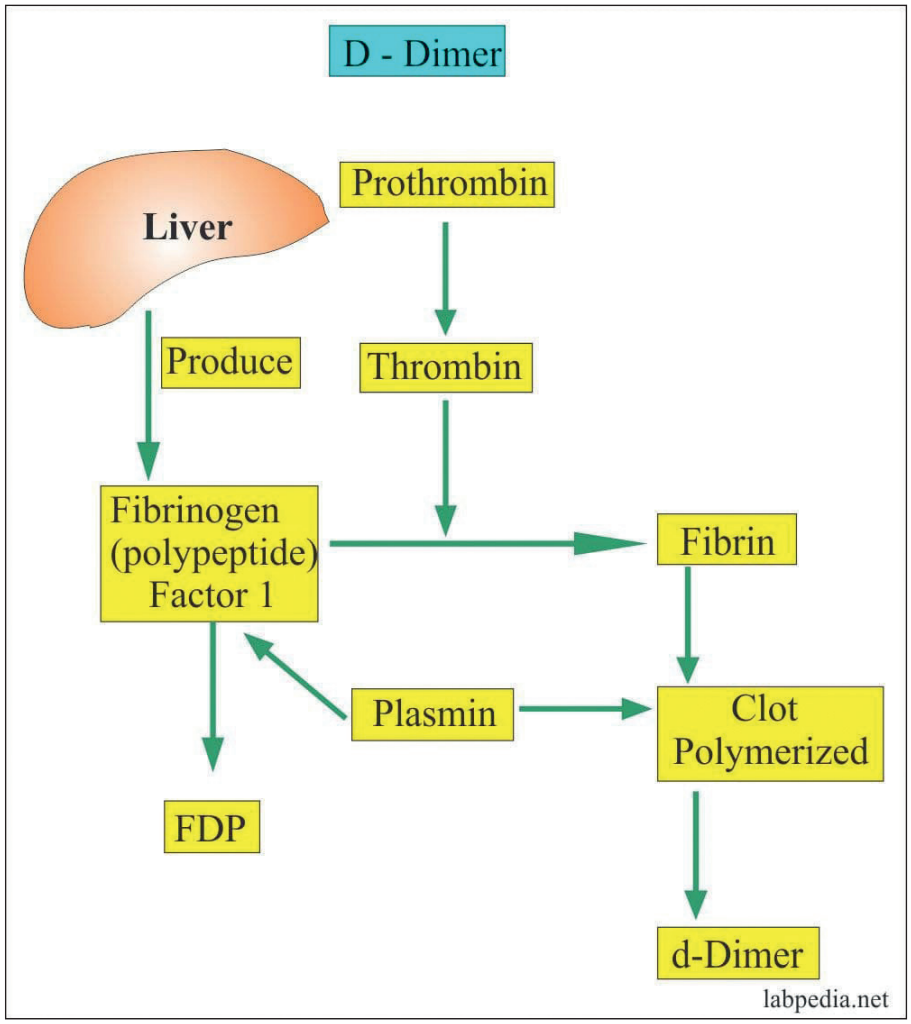

Fig. 1. Pathogenesis scheme of D-Dimer release.

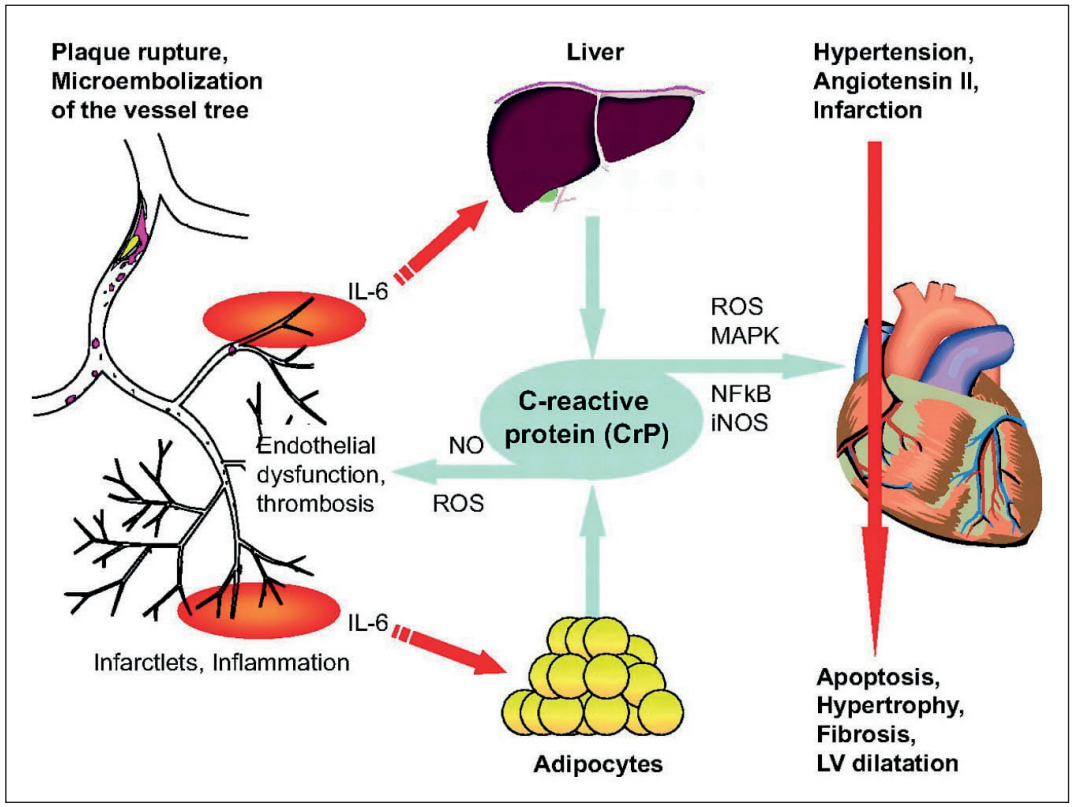

Fig. 2. Pathogenesis scheme of CRP release.

in COVID-19 secondary to increase level of cytokine mainly IL 1,2,6,7,12, tumour necrotic factor and Alfa gamma globulin [13]. In COVID-19 there is unique inflammatory process that leads imbalance between fibrinolysis and coagulation system (Fig. 1, 2) [14].

THE AIM

The aim of this prospective study is to show the values of inflammatory markers (CRP, ESR) in relation to the level of D-Dimer.

Table I. Demographical data distribution of the enrolled patients.

Variables		N	[%]
Age (Mean ± SD)		54.36 ±14.26	
Gender	Male	39	52.7
	Female	35	47.3
D-dimer (Mean ± SD) mcg/mL FEU		0.524 ±0.431	
CRP (Mean ± SD) mg\dl		40.67 ±33.31	
ESR (Mean ± SD) (mm\h)		51.89 ±30.99	

MATERIAL AND METHODS

An analytical cross sectional-observational study was conducted in Basra, starting from August to October involving 74 patients diagnosed with COVID-19 in Al-Mawani Teaching Hospital. All patients included in this study were diagnosed as a COVID-19 and they had two clinical evidence inform of respiratory manifestation and symptoms documented by positive swab and chest CT according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6th edn.) published by the National Health Commission of China [15].

EXCLUSION CRITERIA

Patients who is a known history of seropositivity arthritis (rheumatoid arthritis or high ESR arthritis)

PATIENTS ON ANTICOAGULANT THERAPY

Patients with high risk factors of embolisms seen with contraceptive pills and Antiphospholipid antibody syndrome, agreements of scientific council of anaesthesia and intensive care of Arabic Board of Health Specialization on carrying out this study were acquired before the data collection.

Table II. Demographical data distribution of the enrolled patients to the D-Dimer results.

Variables		Normal D-Dimer	Elevated D-Dimer	p value
Age (Mean ± SD)		51.24 ± 14.78	57.49 ± 13.17	0.059
Gender	Male	19 (51.4%)	20 (54.1%)	0.816
	Female	18 (48.6%)	17 (45.9%)	
CRP (median)		15	50	<0.05
ESR(median)		30	70	<0.05

Table III. Laboratory data distribution of the enrolled patients to the D-Dimer results.

Variables		Normal D-Dimer	Elevated D-Dimer	p-value
CRP	Normal	7 (70%)	3 (30%)	0.254
	Elevated	25 (44.6%)	31 (55.4%)	
ESR	Normal	15(83.3%)	3 (16.7%)	0.004
	Elevated	22 (40.0%)	33 (60%)	

Table IV. Correlations of CRP, ESR and D-Dimer variables in COVID-19 patients.

Variables		ESR	CRP	D-Dimer
ESR	Correlation Coefficient	1.000	0.457 (moderate)	0.354 (moderate)
	P value	.	<0.05	.002
	No.	73	65	73
CRP	Correlation Coefficient	0.457 (moderate)	1.000	.496 (moderate)
	P value	<0.05	.	<0.05
	No.	65	66	66
D-Dimer	Correlation Coefficient	.354 (moderate)	.496 (moderate)	1.000
	P value	0.002	<0.05	.
	No.	73	66	74

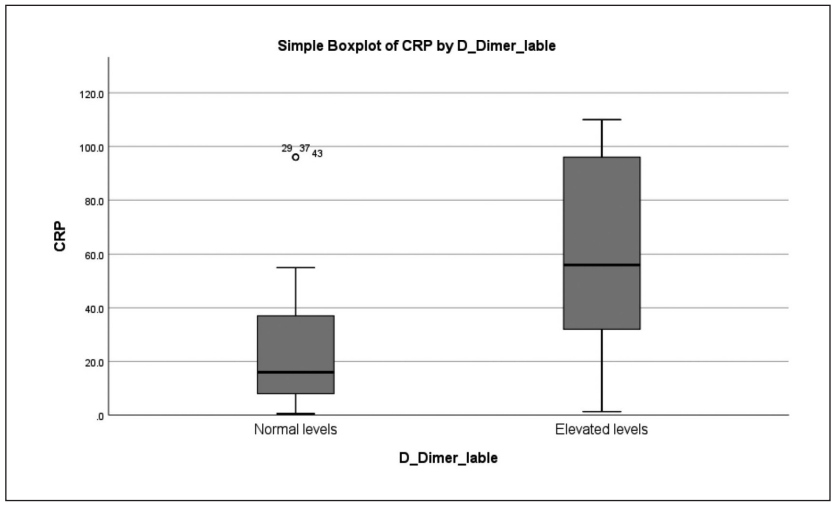

Fig. 3. Box plot of CRP values distribution among D-Dimer results among COVID-19 patients.

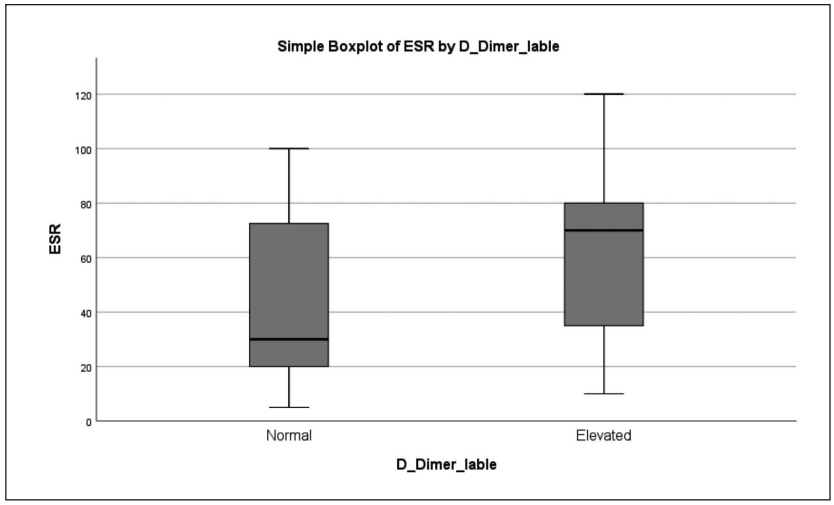

Fig. 4. Box plot of ESR values distribution among D-Dimer results among COVID-19 patients.

Table V. Prediction of CRP, ESR for D-Dimer among COVID-19 patients.

Variables	Coefficient (B)	p value	Lower bound	Upper bound
ESR- D-Dimer	0.096	0.463	-0.163	0.355
CRP- D-Dimer	0.127	0.161	-0.052	0.305

DATA COLLECTION

Data were collected from medical and ICU units. The demographical data (CRP, ESR, and D-Dimer) were collected at the same time.

STATISTICAL ANALYSIS

Data represented as numbers and percentages for categorical variables and medians or mean ± SD for continuous variables, the differences between the groups were calculated using Chi-square test (χ^2) and non-parametric Mann-Whitney U test for abnormally distributed data and independent t test for normally distributed data for categorical and continuous data respectively. Normality in distribution was assessed using Shapiro-Wilk test, and Box plot methods to explore any outliers. Linearity and homoscedasticity were assessed visually by simple histogram chart; nonlinear related data was transformed to Log10 to be fit with the test assumptions. Durbin-Watson statistic was the used test to assess the independence of observations. Simple linear logistic regression test was used to assess the predictive power of the significant variables, in which odds ratio and coefficient value was calculated. Data fitness for the test was checked using Goodness of fit. Non-parametric spearman correlation test was used to calculate the correlation between the variables. Statistical calculations were done using Statistical Package for the Social Sciences version 25 (SPSS Inc.), 95% confidence interval was applied as the dependent interval in statistics, and p values <0.05 were accepted as statistically significant.

RESULTS

Among 74 Covid-19 enrolled patients in this study 52.7% were males to 47.3% females. And the mean ± SD forage, D-Dimer, CRP, and ESR were (54.36 ± 14.26 year, 0.524 ± 0.431, 40.67 ± 33.31, and 51.89 ± 30.99) respectively (Table I)

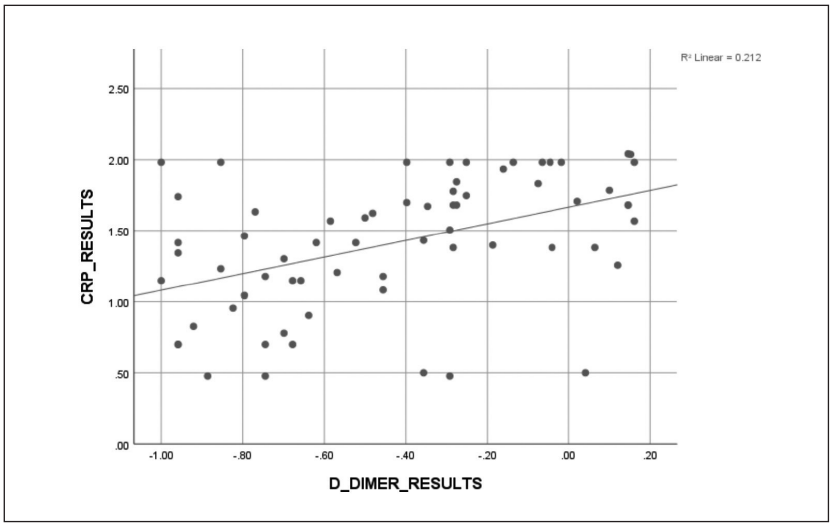

Fig. 5. Scatter dots showing the correlation between CRP and D-Dimer among COVID-19 patients.

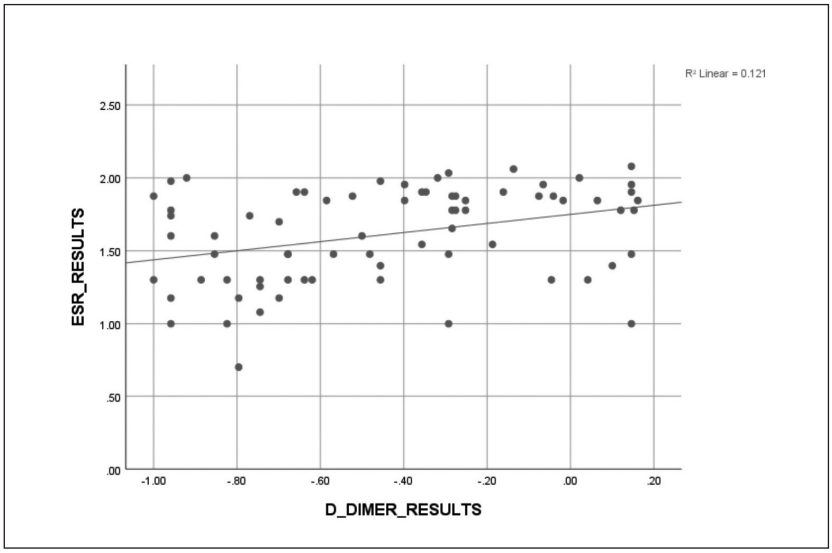

Fig. 6. Scatter dots showing the correlation between ESR and D-Dimer among COVID-19 patients.

The distribution of participant into two main categories according to the D-Dimer levels showed that the median of CRP was (15) for normal levels and (50) for elevated levels, while ESR was (30) for normal levels and (70) for elevated levels and both of them showed a significant differences between the groups, while age and gender had no statistical significant value (Table II)

Chi-square (χ^2) test for ESR data analysis according to D-Dimer levels showed significant differences between the groups (p value 0.004), in contrast to CRP which had no significant results (Table III).

Non-parametric spearman correlation analyses revealed the relationships between D-Dimer levels, ESR and CRP variables studied in COVID-19 patients (Table IV, Fig 3-6). Non-parametric spearman analyses showed that D-Dimer levels moderately correlated with ESR and CRP ($r = 0.354$, $p = 0.002$; $r = 0.457$, $p = <0.05$, respectively).

Simple linear regression test used to assess the predictive ability and the direction of prediction for the significant variables (ESR and CRP), showed that both of them carried a non-significant result (Table V).

DISCUSSION

SARS-CoV-2 infection is a new strain of RNA viruses, which belongs to the β corona virus that characterized by its highly virulent ability [16], which infected about 49.7 million person by themed of 2020 globally, with a mortality rate 0.5%- 8%, as reported by WHO [17]. This new strain of corona viruses attacks the respiratory epithelium by binding to the ACE2 receptors to invade the human body, the progressive events of damages and healing is accompanied by the release of inflammatory markers, such as CRP, D-Dimer, and ESR [18]. Serum D-Dimer is released by the act of plasmin to degrade the fibrin [19], while CRP is a protein synthesised by the liver under the influence of inflammatory signal released by interleukins [20]. Pro-inflammatory cytokines and coagulation cascade activation markers including D-Dimer have been indicated by several studies in China [21-22]. Mo, et al reported the dominance of prothrombotic activity under inflammatory conditions [23]. Demonstration of the correlation between D-Dimer levels and other inflammatory markers associated with COVID-19 infection is still of a limited resources till now. As indicated in the current study, for COVID-19 patients, D-dimer levels

were moderately correlated with higher levels of inflammatory markers including ESR and CRP. In February, 2020 Bilian Yu, et al. conducted a retrospective study on 76 COVID-19 confirmed cases, to investigate the association and correlation of D-Dimer levels with other inflammatory markers,thisstudy-showedthatd-dimerlevelsismoderatelypositivelycorrelated with both of ESR and CRP (r= 0.345, r=0.426) and in spite of several studies reported the association between D-Dimer levels and the prognosis [24-25], this study reported as the first study highlighted the correlation between D-Dimer levels and inflammatory markers [26].The main conflict with Yu's study that can not be ignored is that patients developed thrombotic events didn't excluded from the study, which in turn noted that some patients progressively increased D-Dimer levels with decreased CRP levels, in addition some studies suggested the presence of other factors besides inflammation responsible for the activation of the coagulation pathway and consequence lavation of D-Dimer levels in contrast to the other inflammatory markers [27]. Since, pulmonary embolism is the major life-threatening thrombotic events associated with dysregulation of the coagulation pathway involved in COVID-19 infection progression, and elevated D-Dimer levels is a predictor of underlying this thrombotic alteration, some studies investigate to elaborate the relationship between CRP and D-Dimer levels in patients developed pulmonary embolism phenomenon. In 2009, Siemes, et al. reported a positive correlation between CRP and D-Dimer levels ($r = 0.37$; $p < 0.001$), and both were increased in persons with a pulmonary embolism (CRP: p=0.02; D-dimer: p<0.001) [28]. In 2020, Yumeng Yao, et al in a study established in Wuhan, China on 248 confirmed cases of SARS-CoV-2 infection to elaborate the role of D-Dimer levels in disease progression and its relation to other inflammatory markers, showed that CRP levels increased in consequence with increased D-Dimer levels [29]. Since, COVID-10 infection considered as inflammatory process, so many inflammatory markers will increased progressively, ESR one of these inflammatory indicators, in 2005 Swarts, et al showed that any raised in ESR in any inflammatory process is significantly associated with increased D-Dimer levels [30]. Collectively, the correlation between D-Dimer levels with ESR and CRP is well demonstrated in this study, and it is consistent with previous compared studies. This study has several limitations; firstly, this is a cross-sectional study and participants were from just 1 centres rather than multiple centres, secondly, this study is limited by its small sample size and need to enrol larger sample size for more reliable results, thirdly, in spite that, we found significant correlations, further studies are required to explore the prognostic value of these biomarkers, lastly, heterogeneity of included studies with inadequate evidence may limit the generalizability of our results and that implies the need for further studies.

CONCLUSIONS

In SARS-CoV-2 infection, ESR and CRP levels are moderately positively correlated with D-Dimer, and their increasing levels can be used to predict the synchronized rose of D-Dimer after exclusion the possibility of another inflammatory process that may confound the results.

RECOMMENDATIONS

A large sample study should be contributed in a cohort study to evaluate the exact influence of raising levels of d diner levels on the levels of CRP and ESR. Early administration of anticoagulant in patients with raised levels of ESR and CRP to protect them from the risk of thrombosis.

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