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INCREASES ASPARTATE AMINOTRANSFERASE ACTIVITY NEGATIVELY CORRELATED WITH D-DIMER IN EARLY DIAGNOSED SARS-CoV-2 PATIENTS

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ABSTRACT

SARS-CoV-2 was widely spread early in 2020. It causes unknown pneumonia with different organ complications. An increase in the liver enzymes activity and renal parameters were the most common problems associated with the SARS-CoV-2 infection. Studies reported the correlation between the increase in the liver enzyme activity AST and CRP and ferritin with reporting the correlation with Di-Dimer. This study aims to investigate the correlation between liver enzymes (AST and ALT) and renal parameters with laboratory parameters (D-Dimer, Ferritin, and CRP). Blood samples were withdrawn from 77 (35 controls and 42 patients) to investigate the liver enzymes, renal parameters, blood sugar, and laboratory parameters (D-Dimer, Ferritin, and CRP). The relationship between the increase in the liver enzymes and renal parameters with laboratory parameters increases with the SARS-Co-V-2 infection. 16 (38%) out of 42 patients were associated with severe SARS-CoV-2 illness. Liver enzymes activity ALT and AST were increased in 23 (55%) and 20 (48%) patients respectively. Renal parameters were increased in 16 (38%) patients. Only 11 out of 16 patients were suffering from severe illnesses and had an increase in liver enzymes activity, while only 7 (17%) patients had severe illnesses and an increase in renal parameters. AST activity had a negative correlation with D-Dimer. This study concluded that the increase in AST correlated negatively with the increase in D-Dimer in SARS-CoV-2 patients.

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Introduction

The new strain, positive-sense single-strand RNA, of the SARS virus was discovered later in December 2019, Wuhan, China. It rapidly spread throughout the world and in 2020 the World Health Organisation (WHO) announced it as a global outbreak [1]. SARS-CoV-2 infection is caused by unknown etiology pneumonia with about 85% of asymptomatic patients. Cells with a membrane-bound enzyme angiotensin-converting enzyme 2 (ACE2) receptor are the target of SARS-CoV-2. Alveoli is the main target of SARS-CoV-2. The penetration of the virus to its target cells is mediated by binding the virus spike protein to the ACE2 receptor [2, 3]. Although, ACE2 was found to be expressed on many organs such as the liver, kidney, intestinal, and bladder [4].

SARS-CoV-2 infection stimulates the host immune system which leads to the release of cytokines. Releasing cytokines has many effects on the lungs and other tissues such as the liver and kidney. In the liver, the increase in liver enzymes (Alanine aminotransferase and aspartate aminotransferase) activity has been linked to uncontrolled pro-inflammatory cytokines or liver injury induced by anti-viral drugs [5]. The direct effect of SARS-CoV-2 cannot be ruled out due to high expressions of ACE2 receptors in the liver [4-6]. Moreover, SARS-CoV-19 has been reported to cause kidney injury and this has also been linked to the release of pro-inflammatory cytokines [7-9]. The effects of SARS-CoV-2 on the liver and kidney are still controversial issues. A previous study reported that an increase in AST had a positive correlation with ferritin and C-reactive protein. They did not report the correlation between AST and D-Dimer [10]. The aim of this study was to identify the correlation between the increase in liver enzymes and renal parameters with the increase of laboratory parameters (D-Dimer, Ferritin, and C-reactive protein CRP).

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Materials and Methods

Patients

Blood samples were collected from the seventy-eight participants to investigate the effects of the SARS-CoV-2 infection on some liver and renal parameters. Participants were divided into 2 groups (Control = 35 participants; 19 males and 15 female), (SARS-CoV-2 patients un-hospitalised = 42 participants; 19 males and 21 females). The protocol of this study was reviewed and approved by the ethics committee (IRB) of the College of Science, University of Kufa, Iraq (347/2020), and this is in the agreement with the International Guideline for Human Research, declaration of Helsinki. Informed consent was taken from participants after explaining and clarifying.

Methods

The kits for Aspartate aminotransferase (Cat. No 12211), Alanine aminotransferase (Cat. No 12212), blood urea (Cat. No. 10505), creatinine (Cat. No. 10051), and glucose (Cat. No. 10260) were purchased from the Human Gesellschaft for Biochemical and Diagnostic mbH company, Germany. While other kits such as D-Dimer (Ref. CFPC-25), Ferritin (Ref. CFPC-32), and CRP (Ref. i-CHROMA CRP-25) were purchased from the Boditech Med Incorporated, Republic of Korea. Tests were done following the manufacture's instruction. Data are presented as mean± Standard error. Statistical analyses were performed using GraphPad Prism-8.3. A two-sided *P*-value < 0.05 was considered statistically significant.

Results and Discussion

Seventy-seven participants that were recruited in this study were divided into two groups. Group 1 (control, n=35 participants) and group 2 (early diagnose SARS-CoV-2, n= 42). The mean age of the control group was 37.9±2.28 and 41.38±1.69 for SARS-CoV-2 patients. Female represented 46% (n=16) and 50% (n=21), respectively in both group **(Table 1)**. Our results showed that the SARS-CoV-2 group had a significant increase in D-Dimer 563.88± 48.52 vs 58.86±4.38, Ferritin 522.42±51.48 vs 151.1±6.0, and CRP 59.58±9.15 vs 6.91±0.22 as expected. Many studies reported that SARS-CoV-2 is associated with an increase in liver enzymes [5, 11, 12]. Our results showed that ALT 19.98±1.82 vs 9.73±0.57 and AST 17.31± 1.27 vs 9.74±0.55 were elevated in the SARS-CoV-2 group. Although, renal parameters blood urea 63.27±6.43 vs 34.15±1.61 and serum creatinine 1.24±0.12 vs 0.65±0.06 were also increased significantly in SARS-CoV-2 patients. Hyperglycaemia was not found in both groups **(Table 1)**.

Table 1. Characteristic and distribution of participants according to biomarkers

	Control		**SARS-CoV-2**		P-value
	n= 35		**n= 42**		
	Mean (SE)	**%**	**Mean (SE)**	**%**	
Age (year)	37.9 (2.28)		41.38 (1.69)		.22
Female (no., %)	16	46%	21	50%	
Male (no., %)	19	54%	21	50%	
D-Dimer (ng/ml)	58.86 (4.38)		516.7 (78.23)		.0001
Ferritin (ng/ml)	151.1 (6.04)		522.42 (51.28)		.0001
CRP (mg/dl.)	6.91 (0.22)		59.58 (9.15)		.0001
ALT (U/L)	9.73 (0.57)		19.98 (1.82)		.0001
AST (U/L)	9.74 (0.55)		17.31 (1.27)		.0001
Glucose (fasting) mg/dl	101.77 (1.32)		112 (5.92)		.094
Urea (mg/dl)	34.15 (1.61)		63.27 (6.43)		.0001
Creatinine (mg/dl)	0.65 (0.06)		1.24 (0.12)		.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; M±SE, mean ± standard error.

Next, we tested whether the increase in liver enzyme activity and renal parameters was associated with severe SARS-CoV-2 cases. The severity of the SARS-CoV-2 infection was predicted from CRP level as proposed by Liu *et al*. Liu and colleagues reported that the cut-off value of CRP > 41.8 mg/L is associated with the severe onset of SARS-CoV-2 [13]. Moreover, another study in Italy suggested that the cut-off value >110 mg/L of CRP is associated with severe SARS-CoV-2 infection [14]. In this study our results showed that the severity of this illness was noticed with 16 (38%) out of 42 patients. 6 out of 16 (38%) patients had a high level of D-Dimer and also 6 out of 16 (38%) patients had high ferritin level **(Table 2)**. The increase in ALT and AST activities was noticed in 23 (55%) and 20 (48%) out of 42 patients, respectively. The severity of SARS-CoV-2 was pronounced in 16 out of 42 (38%), and only 11 (69%) out of 16 had high ALT and AST activities **(Table 2)**. Renal dysfunction was noticed in 16 (38%) out of 42 patients with high blood urea and serum creatinine and only 7 (17%) out of 16 patients had

severe illnesses as predicted from CRP. These results indicated that the most severe SARS-CoV-2 could be associated with liver injury but a few cases associated with the renal problem.

Table 2. The number and percentage of SARS-CoV-2 patients with high biomarkers

	SARS-CoV-2		
	Mean (SE)	**No.**	**%**
D-Dimer (ng/ml)	799 (75.75)	19	45%
D-Dimer with severe cases		6	38%
Ferritin (ng/ml)	641 (82.18)	14	74%
Ferritin with severe cases		6	38%
CRP (mg/dl.)	59.58 (9.15)	42	100%
CRP higher than the cut-off		16	38%
ALT (U/L)	27.67 (2.25)	23	55%
ALT with severe cases		11	69 %
AST (U/L)	23.521 (1.6)	20	48%
AST with severe cases		11	69 %
Urea (mg/dl)	98.12 (12.48)	16	38%
Urea with severe cases		7	17%
Creatinine (mg/dl)	2.13 (0.16)	16	38%
Creatinine with severe cases		7	17%

Next, we investigated the correlation between laboratory parameters that increased with SARS-CoV-2, especially CRP, with liver enzymes and renal parameters. Many studies reported that liver enzymes were correlated with inflammatory markers (CRP and ferritin) in SARS-CoV-2 patients [15, 16]. We found that AST had a negative correlation with D-dimer **(Figure 1a)**. Patients with high AST activity seem to have low D-Dimer concentration. The elevation of AST activity and the increase in D-Dimer concentration was noticed in 10 (24%) patients only. Ferritin, like D-Dimer, showed a negative correlation with AST, however, the *P-value* was non-significant (*P*=0.127) **(Figure 1b)**. Neither CRP nor blood urea was correlated with an increase in AST activity **(Figure 1c and 1d**) as proposed by others [10].

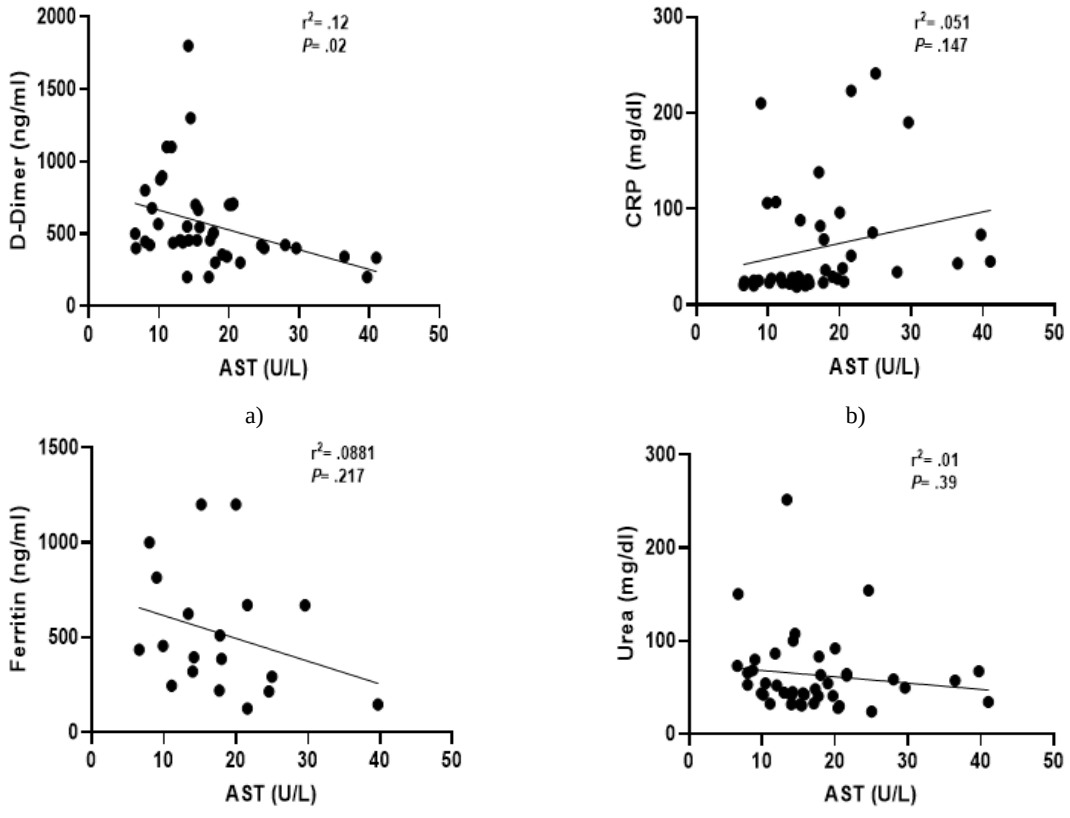


Figure 1. AST correlates with a- D-Dimer but not with b- ferritin, c- CRP, and d- Urea. (n=42 except for ferritin n=19)

The correlation between inflammatory markers was also investigated with ALT. Our results showed that there was no correlation between ALT elevation with CRP **(Figure 2a)**, ferritin **(Figure 2c)**, and blood urea **(Figure 2d)**. ALT negatively correlated with D-dimer, however, it was non-significant **(Figure 2b)**. These results indicated that there is no relation between inflammatory markers and ALT activity.

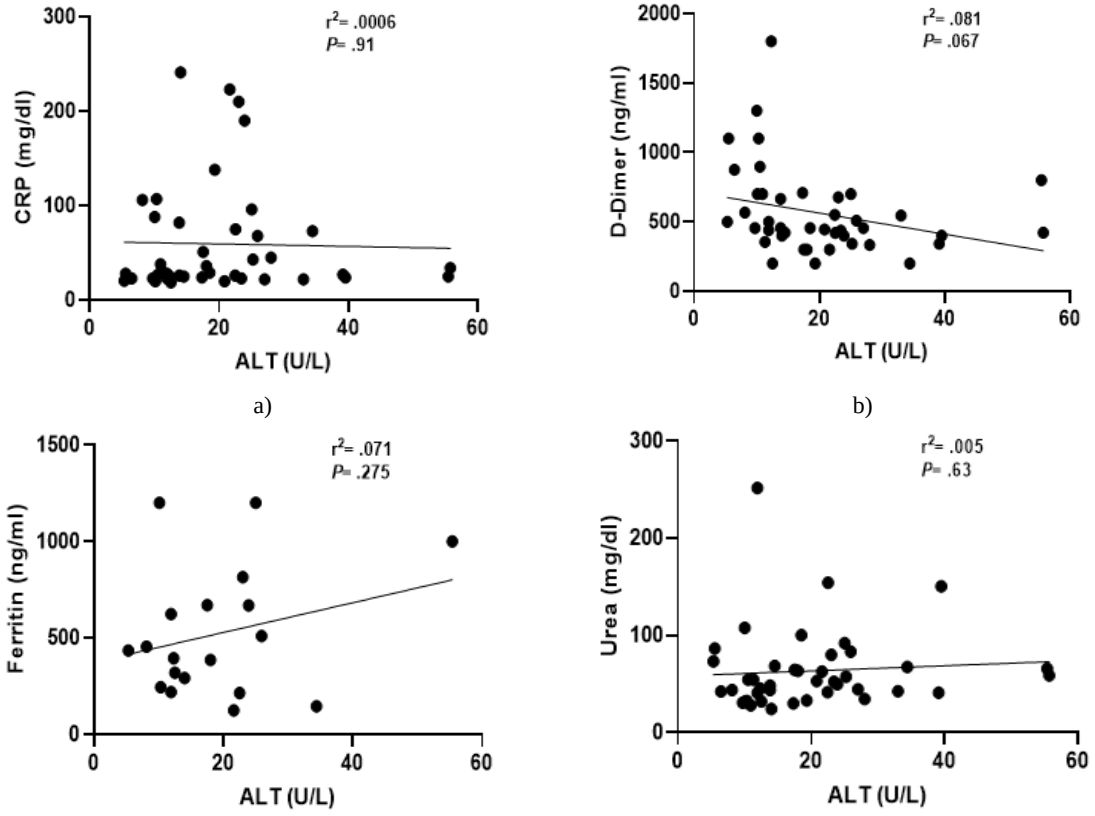
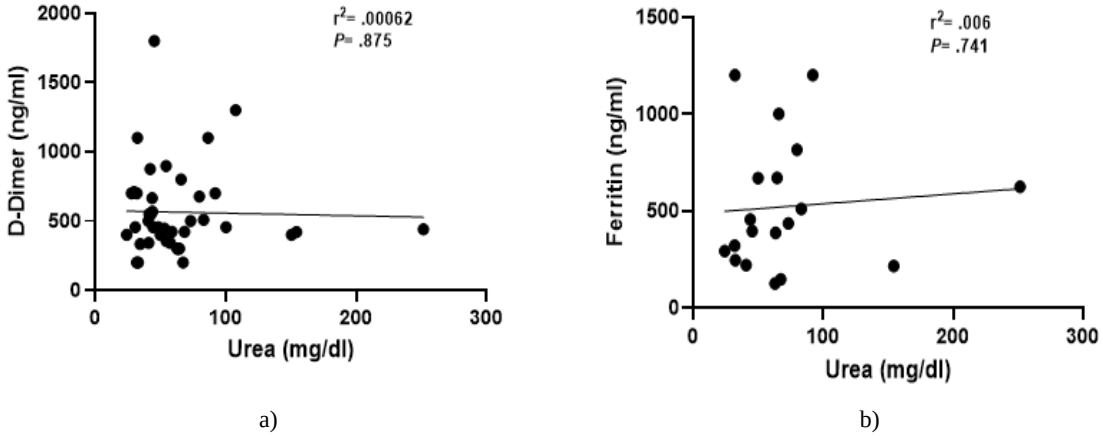


Figure 2. The liver enzyme (ALT) did not correlate with a- CRP; b- D-Dimer; c-Ferritin; and d- Urea. (n=42 except for ferritin n=19).

Within MARS infection renal complications have been reported in Korean patients [17]. It has been reported that SARS-CoV-2 is associated with many organ complications [18]. One of the common complications associated with SARS-CoV-2 is renal disorder. Many studies reported that blood urea increased in SARS-CoV-2 patients [19, 20]. Our results revealed that blood urea and serum creatinine were significantly increased in SARS-CoV-2 **(Table 1)**. Blood urea and serum creatinine were increased in 16 (38%) out of 42 patients **(Table 2)**. Moreover, we investigated the correlation between laboratory markers that increased in SARS-CoV-2 and renal parameters, to understand whether the increase in renal parameters resulted from an increase in laboratory parameters. Our results showed that neither blood urea nor serum creatinine correlated with laboratory markers (D-Dimer, Ferritin, and CRP) **(Figure 3a-3f)**.



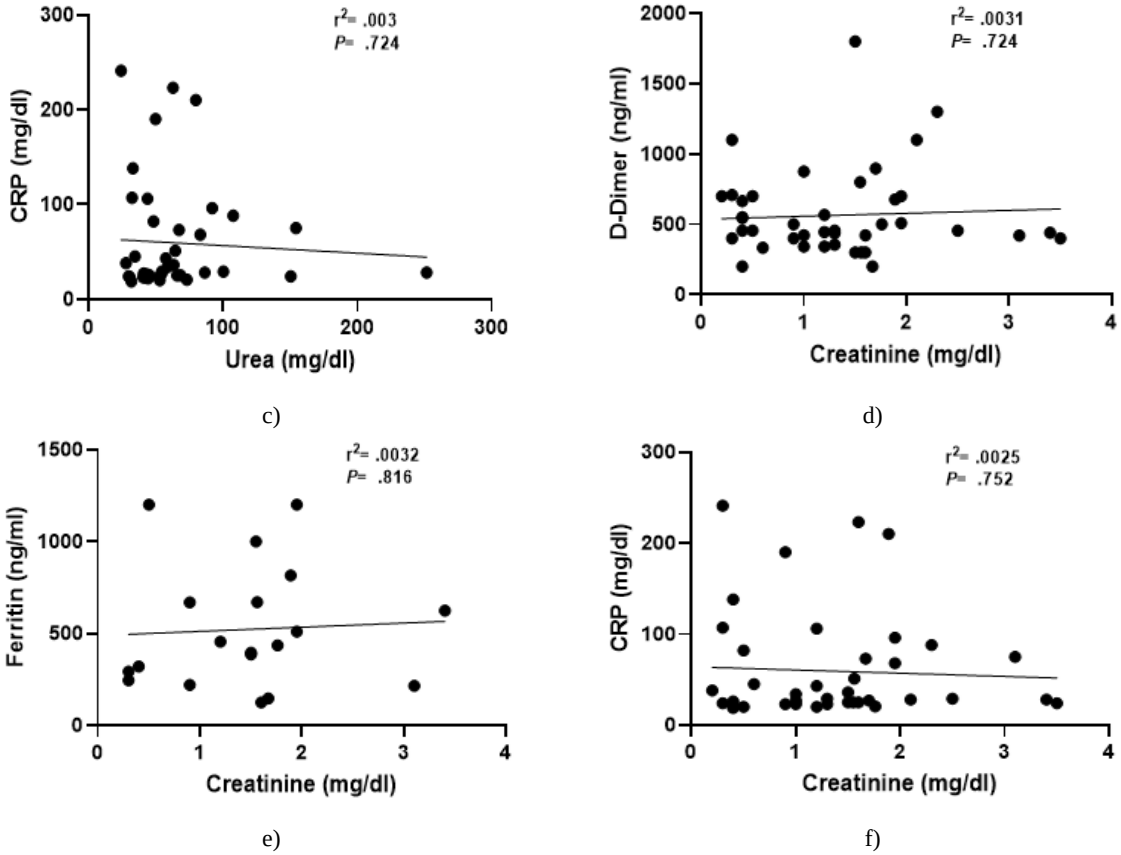


Figure 3. Renal parameters did not correlate with D-Dimer (a and d), Ferritin (b and e), and CRP (c and f). (n=42 except for ferritin n=19).

In December 2019, the novel SARS virus was rapidly spread in China, Wuhan. Later it became a global infection [21-23]. It has been reported that in the early phases of SARS-CoV-2 infection D-dimer, ferritin, and CRP were increased with SARS-CoV-2 patients [24]. D-dimer a fibrin production and degradation due to breakdown of thrombi. It represents the activation of the coagulation system [24-26]. Elevation of D-dimer level is associated with deep vein thrombosis (DVT), pulmonary embolism (PE), surgery, and inflammation [24, 27]. Ferritin is an iron storage protein that is involved in the iron haemostasis mechanism. The increase in ferritin level is associated with many disorders such as coronary artery disease [28]. CRP is a plasma protein in circulation, the cytokine-mediated response of injured tissues increases the concentration of circulating CRP [29, 30]. The level of CRP was increased in all patients as expected. The CRP was recruited to predict the severity of this illness as proposed by another study [13]. Mild illnesses were pronounced in about 26 (62%) patients similar to other studies [31, 32]. This indicated that the severity of SARS-CoV-2 in early diagnose patients are often uncommon or it takes a longer time to display.

A non-specific tissue enzyme AST, which is mostly found in the liver, is also found in other tissues such as the myocardium. It has two isoenzymes found in the cytoplasm and mitochondrial. Measuring the enzyme activity is considered very useful in assessing hepatic liver disorder, alcoholic liver disorder, and in patients with the myocardial disorder [33, 34]. A recent study by Effenberger and colleagues suggested that AST significantly correlated positively with CRP and ferritin. They did not investigate the correlation between AST and D-dimer. Because of the importance of D-Dimer in the prediction of poor prognosis of SARS-CoV-2. We tested the correlation between AST and D-Dimer and our results revealed that there was a negative correlation between AST and D-Dimer. This result could be a good sign to predict that patients with high AST activity might not have high risks of developing poor disseminated intravascular coagulation [35, 36].

The limitations of our study were that we do not have any follow-up information about our patients recruited in this study, and we missed measuring the level of interleukin-6.

Conclusion

We concluded that AST had a negative correlation with D-Dimer in the early diagnosed SARS-CoV-2 patients.

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Conflict of interest: None

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Ethics statement: This study was reviewed and approved by the ethics committee (IRB) of the College of Science, University of Kufa, Iraq (347/2020), and this is in the agreement with the International Guideline for Human Research, declaration of Helsinki.

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