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Endothelial glycocalyx shedding during active COVID-19 infection and its effect on disease severity

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ABSTRACT

Background: COVID-19 pandemic was caused by the SARS-CoV-2 virus that was thought to be associated with microvascular endothelial injury. This study aimed to demonstrate the effect of COVID-19 on markers of endothelial shedding and its effect on patient morbidity and mortality.
Settings and design: This was a prospective cohort study.
Methods: This study was conducted at the isolation hospital at Alexandria Main University hospitals on 40 adult patients infected with COVID-19. Patients were divided according to the severity of the presenting symptoms into two groups; moderate and severe. Serum levels of Syndecan-1 and Heparan sulfate were measured at hospital admission and at the end of the first week. Clinical and demographic data along with laboratory investigations and outcomes were compared between the two groups.
Results: Our results indicated that patients with severe symptoms of COVID-19 had notably high levels of syndecan-1 and Heparan sulfate compared to patients with moderate symptoms on day 1 and day 7. Further investigations revealed that D-dimer, CRP, and IL-6 levels in patients with severe symptoms were higher in patients with severe symptoms. Our results also indicated that IL-6 increased on day 4 and gradually decreased on day 7 in both groups. Furthermore, serum levels of Syndecan-1, Heparan sulfate, D-dimer, and CRP decreased gradually from day 1 to day 7 in both groups. There was an association between markers of endothelial shedding with thrombotic and cardiovascular complications. It seems that the serum Syndecan-1 and Heparan sulfate might be good candidates to monitor COVID-19 activity.
Conclusion: Patients with severe symptoms of COVID-19 have high serum levels of syndecan 1 compared to patients with moderate symptoms and have higher mortality and more prolonged hospital stay due to more endothelial injury and inflammatory reaction. Syndecan-1 may be used to monitor disease progression and severity.

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Coronavirus disease; endothelial shedding; syndecan-1; heparan sulfate

1. Introduction

The coronavirus disease pandemic, which was reported by the World Health Organization in 2019, was caused by the severe acute respiratory syndrome coronavirus. It led to enormous deaths around the whole world with a mortality rate of about 30% of ICU patients [1,2].

Multiple studies have found a rise in the occurrence of thrombotic complications in COVID-19 patients, carried on changes in levels of D-dimer, antithrombin, and fibrinogen degradation products; therefore, a prothrombotic state of COVID-19 pathogenesis has been considered [3,4].

COVID-induced coagulopathy may be related to platelet over-reactivity, hypercoagulability, hypo-fibrinolysis, complement system activation, and derangement in the RAAS system in the presence of endothelial injury caused by the underlying inflammation [5].

The SARS-CoV-2 virus enters the infected patient cells where it binds to the ACE2 receptor which is present in the endothelium of many tissues. ACE2 functions as a peptidase that cleaves angiotensin-II. Elevated levels of angiotensin (Ang-II) increase oxidative stress and dysfunction of the endothelial cell through the production of superoxide anion. So, the binding of the virus to ACE2 may lead to angiotensin induced injury of the endothelial wall that has been detected in the autopsies of COVID-19 patients' lungs [6].

The endothelial glycocalyx (EGX) has two main components, glycosaminoglycans (GAGs) and proteoglycans (PGs). The main PGs are syndecans which bind several GAGs, mainly Heparan sulfate (HS). The EGX has an important role to regulate coagulation, inflammation, and microvascular permeability [7,8].

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Fraser et al. investigated the role of Syndecan-1 in COVID-19 pathophysiology, and they found that inflammation-induced shedding of the glycocalyx contributes to microvascular pathology in COVID-19 patients [9].

As microvascular endothelial shedding is the main involved pathogenesis in COVID-19 which leads to bad consequences. Therefore, it is crucial to define the value of endothelial injury biomarkers in determining COVID-19 severity. The aim of the study was to determine the effect of active COVID-19 infection on some markers of endothelial shedding and to correlate these changes with patients' morbidity and mortality.

2. Patients and methods

After approval from the local ethics committee, informed consent was taken from each patient. The study was carried out at the isolation hospital at Alexandria Main University hospitals on 40 adult patients infected with COVID-19.

2.1. Sample size calculation

A minimum total sample size of (40) COVID-19 patients were needed to [10]:

(1) Detect a difference of (13) ng/ml in mean Heparan sulphate between a group with severe COVID-19 infection and another group with mild infection using a standard deviation of (11 and 4 respectively), a two-sided independent t-test, a significance level of 0.05 and 90% power.
(2) Detect a difference of (80) ng/ml in mean Syndecan-1 level between both groups using group standard deviation of (100 and 51 respectively); a two-sided Mann–Whitney test, a significance level of 0.05 and 90% power.
(3) Assess the use of Heparan sulfate as a marker for prediction of development of COVID-19 induced organ dysfunction using AUC = 0.88, ROC curve analysis, a significance level of 0.05 and 80% power.

2.2. Patients were divided into two groups

2.2.1. Group I

Patients with positive PCR for COVID-19 who had moderate symptoms (symptoms of lower respiratory tract disease and saturation of oxygen on room air ≥94%).

Table 1. Comparison between the two studied groups according to demographic data, comorbidities, mean oxygen saturation on day 1, the needs for mechanical ventilation, mortality, length of hospital stay and ICU stay.

	Group I ($n = 22$)	Group II ($n = 18$)	Test of Sig.	p
Age (years)				
Mean ± SD.	58.8 ± 14.6	65.8 ± 14.8	t=1.503	0.141
Sex				
Male	12 (54.5%)	7 (38.9%)	χ^2=0.973	0.324
Female	10 (45.5%)	11 (61.1%)		
Weight (kg)				
Mean ± SD.	90 ± 9.90	86.9 ± 10.5	t=0.944	0.351
Comorbidities	20 (90.9%)	15 (83.3%)	$\chi^2 = 0.519$	$^{FE}p = 0.642$
Hypertension	15 (68.2%)	10 (55.6%)	$\chi^2 = 0.673$	0.412
Diabetes	9 (40.9%)	7 (38.9%)	$\chi^2 = 0.017$	0.897
Cardiac	4 (18.2%)	2 (11.1%)	$\chi^2 = 0.388$	$^{FE}p = 0.673$
Respiratory	1 (4.5%)	3 (16.7%)	$\chi^2 = 1.616$	$^{FE}p = 0.310$
CKD	2 (9.1%)	1 (5.6%)	$\chi^2 = 0.178$	$^{FE}p = 1.000$
Cancer	3 (13.6%)	2 (11.1%)	$\chi^2 = 0.058$	$^{FE}p = 1.000$
Collagen	2 (9.1%)	2 (11.1%)	$\chi^2 = 0.045$	$^{FE}p = 1.000$
Others	2 (9.1%)	7 (38.9%)	$\chi^2 = 5.041$	$^{FE}p = 0.053$
Oxygen saturation at room air % on day 1				
Mean ± SD.	93.95 ± 2.38	81.1 ± 6.13	t= 8.422*	<0.001*
Needs for MV during hospitalization	5 (22.7%)	8 (44.4%)	$\chi^2 = 2.128$	0.145
Needs for MV in first week	2 (9.1%)	3 (16.7%)	$\chi^2 = 0.519$	$^{FE}p = 0.642$
Hospital stay (days)				
Mean ± SD.	12.2 ± 4.32	16.5 ± 6.21	U=111.5*	0.017*
Length of ICU stay (days)				
Mean ± SD.	9.32 ± 4.36	15.7 ± 6.21	U=77.0*	0.001*
Mortality				
No	17 (77.3%)	10 (55.6%)	χ^2=2.128	0.145
Yes	5 (22.7%)	8 (44.4%)		

SD: standard deviation;U: Mann–Whitney test; t: Student t-test.
χ^2: Chi square test; FE: Fisher Exact.
p: *p* value for comparing between the two studied groups.
*:Statistically significant at $p \leq 0.05$.
Group I: Patients with moderate symptoms.
Group II: Patients with severe symptom.

2.2.2. Group II

Patients with positive PCR for COVID-19 who had severe symptoms (patients had oxygen saturation on room air <94%, PaO2/FiO2 ratio <300 mm Hg, respiratory rate >30 per minute, or infiltrations in lung involving >50%).

Exclusion criteria included patient refusal and patients aged less than 18 years.

PCR was used to confirm COVID-19 infection after admission to the isolation hospital. According to the National Health Committee of Egypt's COVID-19 diagnosis and treatment plan, patients received oxygen therapy, antiviral, and other supportive treatment.

Blood samples were collected using EDTA as an anticoagulant. Samples were centrifuged at 2000–3000 RPM at 2–8°C within 30 min of collection. Plasma was isolated and then frozen at–20°C. Plasma concentrations of syndecan-1 and Heparan sulfate were measured using enzyme-linked immunosorbent assay (ELISA) with a commercially available kit at the following points: at hospital admission and the end of the first week in the hospital.

Routine laboratory tests were obtained and recorded daily, including a complete blood picture, coagulation profile, renal functions, and liver function testing. Other investigations, including D-dimer, CRP, interleukin-6, and procalcitonin, were measured at three time points: at admission, 4th and 7th days of hospitalization.

Patients' demographic data including age, sex, weight, and comorbidities were recorded.

Oxygen supply, chest CT findings, and the need for invasive mechanical ventilation were also recorded.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated to assess illness severity at admission and during hospitalization. The thrombotic complications and cardiovascular complications were documented. The length of intensive care stay and hospitalization were recorded.

The primary aim of the current study was to demonstrate the effect of active COVID-19 infection on markers of endothelial shedding. The secondary outcome was to correlate these changes to other laboratory investigations and to the patients' morbidity and mortality.

2.3. Statistical analysis

Data were entered into the computer and then analyzed using version 20.0 of the IBM SPSS software package. *(IBM Corp., Armonk, NY)* [11].

Table 2. Comparison between the two studied groups according to plasma level of Syndecan-1, Heparan sulfate, D-dimer, Interleukin-6, Procalcitonin and CRP.

		Group I (n = 22)	Sig.	Group II (n = 18)	Sig.	U	p
Syndecan-1 (ng/ml)	**Day 1**						
	Mean ± SD.	117 ± 54.3		160 ± 69.5		100.0*	0.007*
	Day 7						
	Mean ± SD.	98 ± 62	p_0=0.012*	133 ± 53.0	p_0=0.012*	82.0*	0.001*
Heparan sulfate (ng/ml)	**Day 1**						
	Mean ± SD.	4.68 ± 1.33		6.89 ± 2.81		85.0*	0.002*
	Day 7						
	Mean ± SD.	3.31 ± 1.19	p_0=<0.001*	5.14 ± 3.71	p_0=0.007*	119.0*	0.032*
D-dimer (ug/l)	**Day 1**						
	Mean ± SD.	3402 ± 11241		5930 ± 8856		85.50*	0.002*
	Day 4						
	Mean ± SD.	2243 ± 6183	p_1=0.024*	3816 ± 5197	p_1=0.046*	76.0*	0.001*
	Day 7						
	Mean ± SD.	1781 ± 2952	p_1<0.001*	3139 ± 4431	p_1<0.001*	92.0*	0.003*
Interlukin-6 (pg/ml)	**Day 1**						
	Mean ± SD.	34.8 ± 39.5		90.7 ± 66		93.0*	0.004*
	Day 4						
	Mean ± SD.	47.5 ± 60.3	p_1=0.007*	139.9 ± 151.5	p_1=0.010*	81.0*	0.001*
	Day 7						
	Mean ± SD.	29.6 ± 65.9	p_1=0.024*	54.7 ± 35	p_1=0.020*	79.50*	0.001*
Procalcitonin (ng/ml)	**Day 1**						
	Mean ± SD.	0.181 ± 0.199		0.181 ± 0.176		184.5	0.717
	Day 4						
	Mean ± SD.	0.326 ± 0.404	p_1>0.05	0.292 ± 0.380	p_1=0.677	189.0	0.819
	Day 7						
	Mean ± SD.	0.938 ± 1.616	p_1>0.05	0.856 ± 0.968	p_1=0.001*	154.5	0.240
CRP (mg/l)	**Day 1**						
	Mean ± SD.	38.3 ± 38.6		94.3 ± 81.1		96.5*	0.005*
	Day 4						
	Mean ± SD.	36.4 ± 54	p_1=0.451	62.4 ± 63.7	p_1=0.005*	118.0*	0.030*
	Day 7						
	Mean ± SD.	25.7 ± 33	p_1=0.002*	44.8 ± 38.9	p_1<0.001*	99.5*	0.006*

SD: standard deviation; U: Mann–Whitney test; p: p value for comparing between the two studied groups*: Statistically significant at p ≤ 0.05 p_0: p value for Wilcoxon signed ranks test for comparing between Day 1 and Day 7.

p_1: p value for Post Hoc Test (Dunn's) for Friedman test for comparing between Day 1 and each other periods.

The qualitative data were categorized into numbers and percentages. Shapiro–Wilk test was used to demonstrate the normality of distribution. Mean, standard deviation, and median were used to describe quantitative data. The obtained results were judged to be significant at the 5% level. For categorical variables, we used the Chi-square test to differentiate between different groups. Normally distributed quantitative variables were compared between the two study groups using the Student's t-test. To compare between more than two periods for normally distributed quantitative variables, ANOVA with repeated measures was used, along with the PostHoc test for pairwise comparisons. For quantitative variables with abnormally distributed distributions, the Mann–Whitney test was used to compare two study groups. For quantitative data with abnormal distribution, the Wilcoxon signed rank test was utilized to compare between two periods.

Friedman test and Post Hoc Test (Dunn's) were used to compare between more than two periods for quantitative variables with abnormal distributions. The Spearman coefficient test was used for the correlation between two abnormally distributed quantitative variables.

3. Results

As shown in Table 1, no statistically significant difference was found between moderate and severe groups regarding age, sex, weight, and associated comorbidities. Regarding hemodynamic monitoring, there was a significant difference between the two groups in oxygen saturation at admission and during

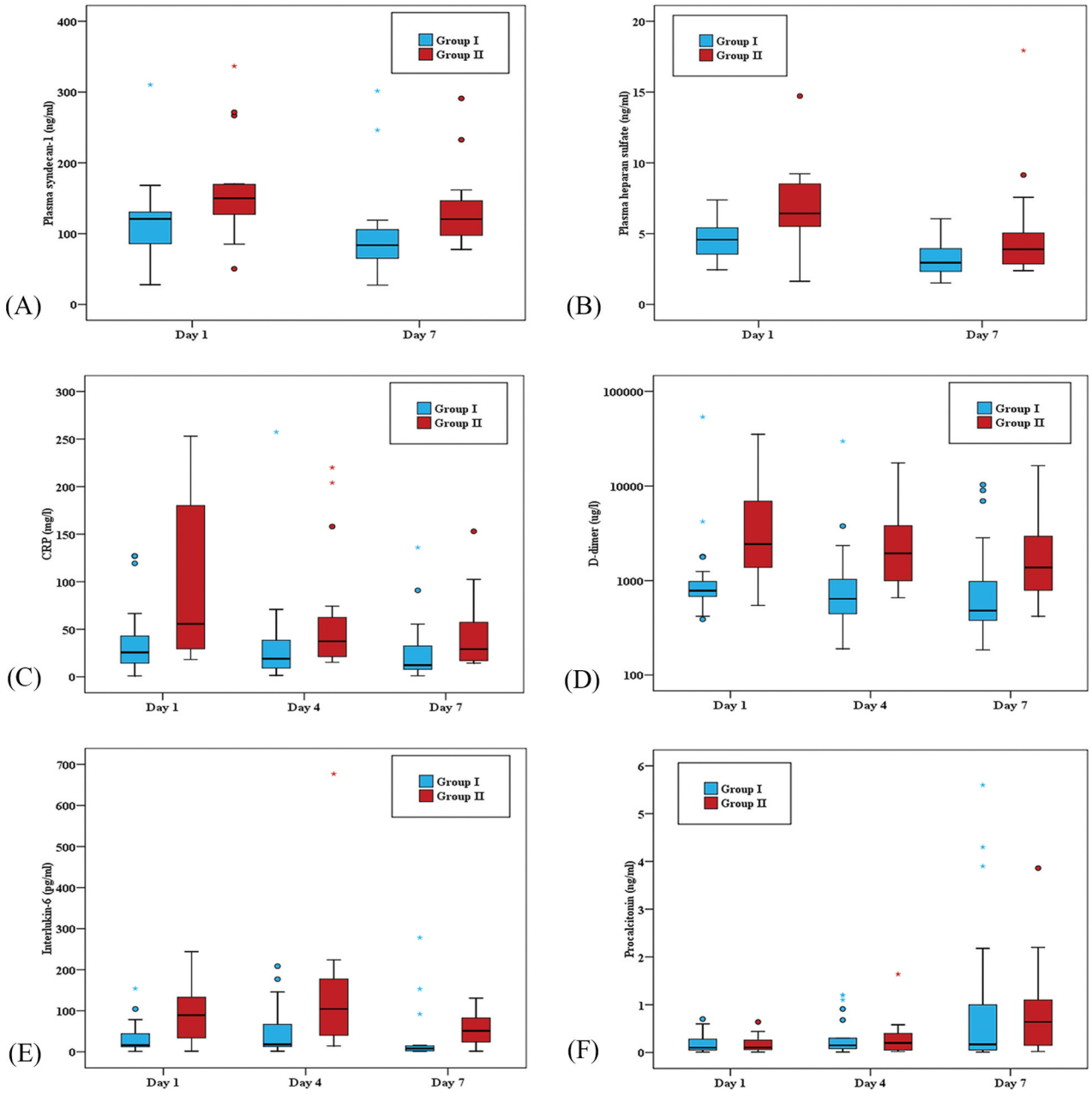

Figure 1. The comparison between changes in the SDC-1, H.S, CRP, D-dimer, IL-6 and procalcitonin between the two groups.

hospitalization while there was no difference in heart rate and blood pressure during hospitalization. Also, our study demonstrated a significant difference between the two groups with regard to some laboratory findings as urea and lymphocytes (Ps: 0.042, 0.009), while other parameters such as platelets, prothrombin time, partial thromboplastin time, creatinine, ALT, AST, and albumin showed no significant difference (Table 2). Also, our study showed a significant difference between both groups in hospital stay and ICU stay (Ps: 0.017, 0.001 respectively). Typical CT chest findings were compared between the two groups. That findings included bilateral, peripheral ground-glass opacities and consolidative pulmonary infiltrates. There was a statistically significant difference between the two groups regarding the presence of typical CT findings. ($p = 0.027$)

The present study also showed that the serum levels of syndecan-1, Heparan sulfate, D-dimer, IL-6, and CRP were significantly higher in patients with severe symptoms on days 1, 4, and 7. Procalcitonin showed no significant difference between the two groups (Table 2).

We also compared the temporal changes in the levels of syndecan-1, Heparan sulfate, D-dimer, CRP, IL-6, between the two groups, and we found that Serum levels of syndecan-1, Heparan sulfate, D-dimer, and CRP were significantly higher in patients with severe symptoms than those with moderate symptoms at the time of hospitalization (Ps: 0.007, 0.002, 0.002, 0.005 respectively); however, there was a gradual decrease of their level from the admission day to day 7. IL-6 was significantly higher in group 2 than in group 1 ($P < 0.004$). Also, the levels of IL-6 in both groups gradually increased from the day of admission to day 4 and then gradually decreased on day 7 (Figure 1).

Further analysis in the current study indicated that the dead patients had significantly high levels of Syndecan-1, Heparan sulfate, D-dimer, IL-6, and CRP compared to live patients (Ps: 0.07, 0.02, 0.011, 0.001, 0.014 respectively). Moreover, it showed that D-dimer, IL-6, and CRP, levels in dead patients were significantly higher than those alive on days 1, 4, and 7. Also, serum levels of syndecan-1 and Heparan sulfate were higher in dead than in live patients on day 1 and day 7. Besides, APACHE 2 score was significantly higher in dead than in live patients at admission and day 6 (Ps: 0.025, 0.001 respectively) (Table 3).

Table 3. Relation between mortality and different parameters (syndecans-1, heparan sulfate, D-dimer, Interleukin-6, CRP and APACHE II score).

	Mortality			
	No ($n = 27$)	Yes ($n = 13$)	U	P
Plasma syndecan-1 (ng/ml)				
Day 1				
Mean ± SD.	110.2 ± 35.66	191.0 ± 77.18	49.50*	<0.001*
Day 7				
Mean ± SD.	99.0 ± 42.88	145.0 ± 78.81	107.0*	0.049*
Heparan sulfate (ng/ml)				
Day 1				
Mean ± SD.	5.05 ± 1.80	6.98 ± 2.93	100.0*	0.029*
Day 7				
Mean ± SD.	3.47 ± 1.51	5.53 ± 4.09	90.50*	0.013*
D-dimer (ug/l)				
Day 1				
Mean ± SD.	3882 ± 10722	5907 ± 9243	88.0*	0.011*
Day 4				
Mean ± SD.	2572 ± 6332	3737 ± 4399	56.0*	<0.001*
Day 7				
Mean ± SD.	1461 ± 2780	4326 ± 4673	50.0*	<0.001*
Interlukin-6 (pg/ml)				
Day 1				
Mean ± SD.	35.02 ± 39.23	111.82 ± 61.81	50.0*	<0.001*
Day 4				
Mean ± SD.	51.56 ± 57.53	167.02 ± 170.37	72.0*	0.002*
Day 7				
Mean ± SD.	18.91 ± 23.90	86.67 ± 72.57	48.0*	<0.001*
CRP (mg/l)				
Day 1				
Mean ± SD.	52.24 ± 62.89	86.92 ± 71.07	91.50*	0.014*
Day 4				
Mean ± SD.	43.72 ± 64.47	57.18 ± 47.57	89.500*	0.012*
Day 7				
Mean ± SD.	22.92 ± 31.76	57.90 ± 35.59	44.0*	<0.001*
APACHE II Score				
At admission				
Mean ± SD.	7.89 ± 3.60	12.08 ± 5.91	98.500*	0.025*
Day 6				
Mean ± SD.	4.04 ± 2.67	11.38 ± 6.49	45.500*	<0.001*

SD: standard deviation U: Mann–Whitney test p: p value for comparing between mortality or not.
*Statistically significant at $p \leq 0.05$.

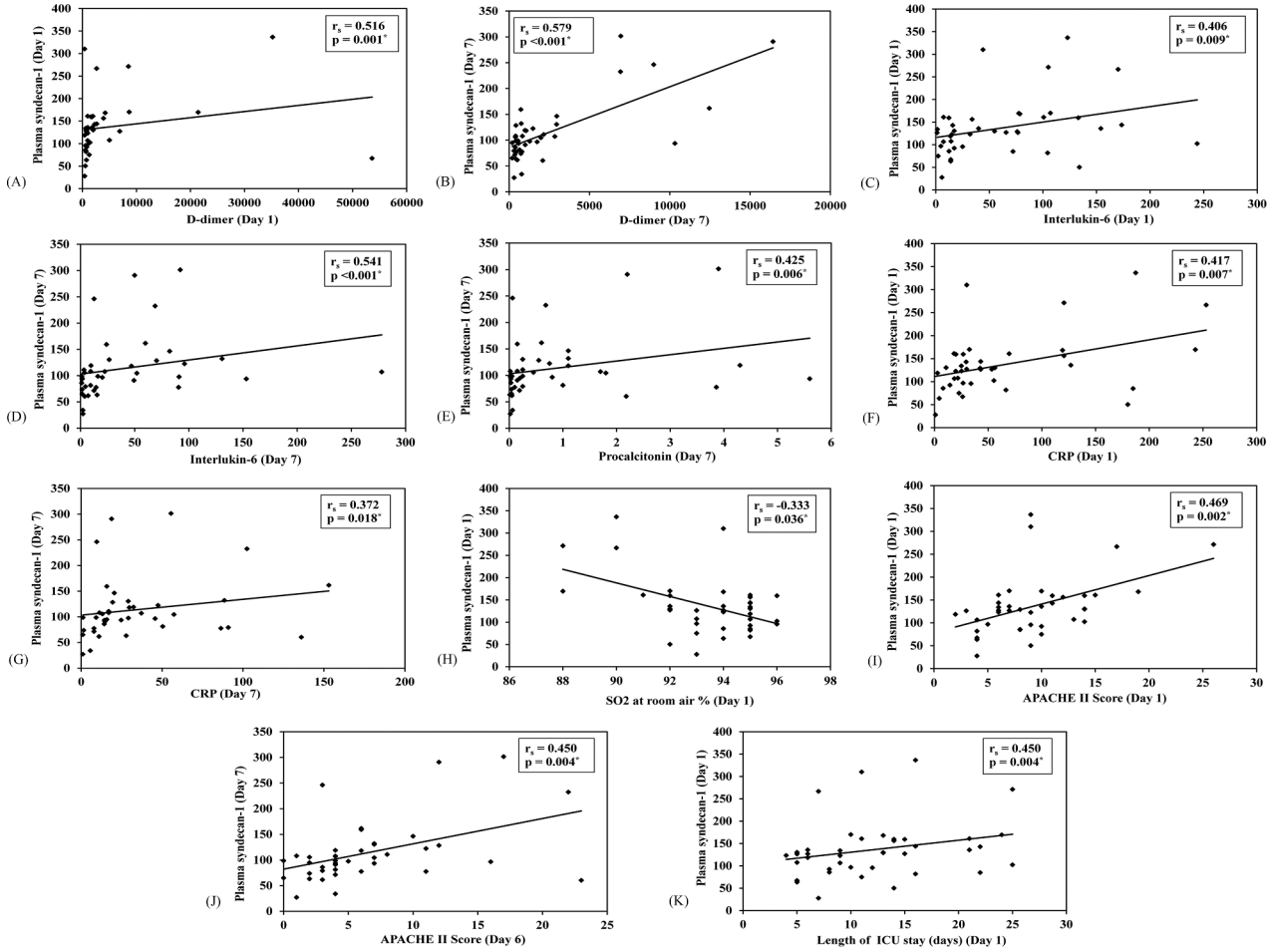

Figure 2. The correlation between syndecan-1 and other parameters. It showed a positive correlation with CRP, D-dimer, IL-6, APACHE score and length of hospital stay. SDC-1 was negatively correlated with oxygen saturation.

Our study also showed that Syndecan-1 and Heparan sulfate were positively correlated with IL-6, CRP, and D-dimer on both day 1 and 7. Our results showed a positive correlation between markers of endothelial shedding with APACHE 2 score and length of ICU stay. Also, there was a negative correlation between syndecan-1 and oxygen saturation at the time of admission (Figures 2, 3).

Regarding the incidence of thrombotic complications, our study showed that there was an association between syndecan-1 and thrombotic complications on day 1 and day 7 (Ps: 0.02, 0.048 respectively). Furthermore, there was an association between the Heparan sulfate levels with thrombotic complications on day 1 and with cardiovascular complications on day 7 (Ps: 0.035, 0.007 respectively). ROC curve analysis demonstrated that the SDC-1 and Heparan sulfate were significantly different between the two groups. Also, according to the ROC curve analysis results, the areas under the curve (AUC) of SDC-1 and Heparan sulfate on day 1 were 0.747 and 0.785, respectively. It revealed an optimal cut-off value of SDC-1 (129.296 ng/ml) and Heparan sulfate (5.419 ng/ml) to distinguish moderate from severe cases. In brief, the ROC result indicated that the SDC-1 with Heparan sulfate might be good candidates to monitor COVID-19 severity.

4. Discussion

The novel pandemic infectious disease COVID-19 is characterized by rapid transmission and is accompanied by high mortality that may reach 31% in ICU-admitted patients (2). While there is still a lack of evidence of the actual pathophysiology of the COVID-19 disease state, it is rather difficult to address appropriate management plans [12]. Many investigations have been launched to determine the pathogenesis of COVID-19. Two studies reported SDC-1, a marker of endothelial shedding in patients infected with COVID-19 [9,13]. Fraser et al. showed that patients who were admitted to the ICU had high levels of syndecan-1 and hyaluronic acid [9], while Hutchings et al. showed that syndecan-1 levels were slightly increased in critical patients compared to controls [13]. Given the dilemma on the role of syndecans-1 during the course of COVID-19, in our research, we explore temporal changes in markers of

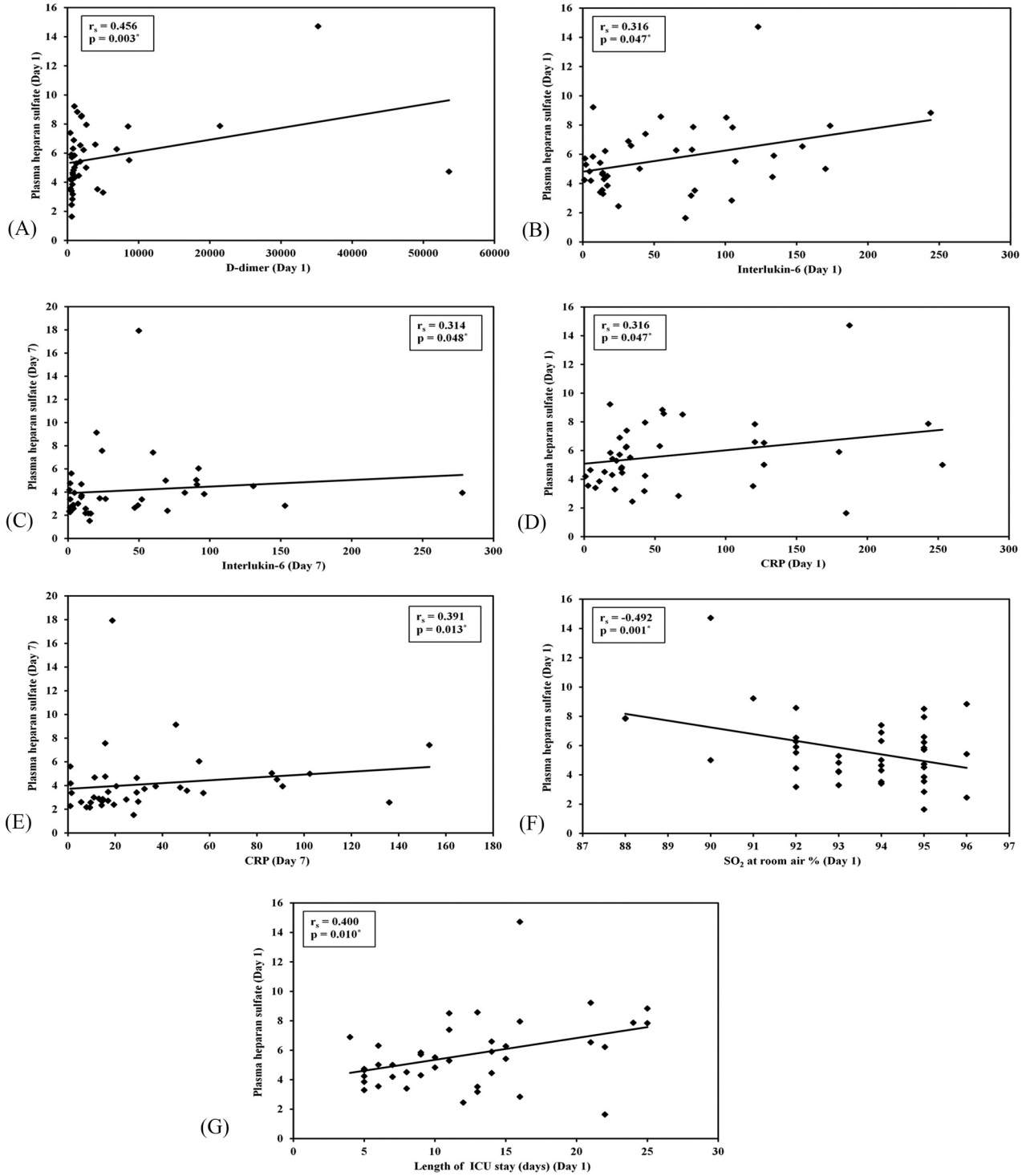

Figure 3. The correlation between heparan sulfate and other parameters. H.S was positively correlated with D-dimer, IL-6, CRP and length of ICU stay. Also H.S was negatively correlated with oxygen saturation.

endothelial shedding in moderate and severe cases along with other markers including D-Dimer, IL-6, procalcitonin, CRP. Moreover, we correlate these changes to patients' morbidity and mortality.

The present study indicated that serum levels of Syndecan-1 and Heparan sulfate in patients with severe symptoms of COVID-19 were significantly higher than those with moderate symptoms. Also, there was a gradual decrease in the level of SDC-1 with disease progression from the day of admission to day 7 in both groups.

The glycocalyx is a gel-like layer that surrounds all living cells. It is composed of glycosaminoglycans (GAGs) and proteoglycans (PGs). The PGs are syndecans that are bound to several GAGs, mainly Heparan sulfate (HS) and Chondroitin sulfate. The vascular endothelial glycocalyx has an important role to inhibit

intravascular coagulation and maintain microvascular permeability [7,8,14].

Our study showed that there was an association between syndecan-1 and thrombotic complications on day 1 and day 7. Furthermore, there was an association between the Heparan sulfate level with thrombotic complications on day 1 and with cardiovascular complications on day 7. This indicated that COVID-19 is a systemic disease associated with endothelial dysfunction and inflammation. However, it is still unclear to determine whether this virus directly activates the coagulation cascade or whether other mechanisms are involved [15].

The virus triggers systemic inflammation and causes lesions in blood vessels. The ACE2 receptor as a SARS-CoV-2 receptor is located on the vascular lining of endothelial cells and arterial smooth muscle cells. Consequently, SARS-CoV-2 directly adheres to vascular endothelium causing endothelial dysfunction, which is followed by microvascular leakage, intravascular coagulation, and release of inflammatory cytokines [16].

The present study also revealed that serum levels of markers of inflammation such as IL-6 and CRP along with D-dimer were significantly increased in patients with severe symptoms than those with moderate symptoms. We have also indicated that the IL-6 level increased from the day of admission to day 4 in both groups and then gradually decreased from day 4 to day 7. However, the D-dimer and CRP levels gradually decreased from day 0 to day 7 in both groups of patients. In agreement with our results, these studies showed that the IL-6 [8,17–23], D-dimer [24,25], and CRP [26–28] were elevated in patients with COVID-19.

Further analysis revealed that serum levels of inflammatory markers including IL-6, CRP, along with D-dimer were significantly elevated in dead patients than those alive. Also, serum levels of syndecan-1 and Heparan sulfate were higher in dead than in alive patients on day 1 and day 7. Besides, APACHE 2 score was significantly elevated in dead than in alive patients at admission and day 6.

As results showed, the levels of Syndecan-1 and Heparan sulfate were positively correlated with markers of inflammation including IL-6, CRP, and with D-dimer. This may be explained by the compensatory response of syndecans to alleviate the inflammatory response provoked by SARS-CoV-2. Our results showed a positive correlation between markers of endothelial shedding with APACHE 2 score and length of ICU stay. Also, there was a negative correlation between syndecan-1 and oxygen saturation at the time of admission.

A high serum level of Syndecan-1 reveals more severe endothelial injury and more glycocalyx shedding. The higher mortality in patients with high serum levels of syndecan-1 suggests that preserving glycocalyx function may be an option in COVID-19 treatment. Multiple studies have discussed that, but there are no clear conclusions yet [29,30].

5. Conclusion

Vascular endothelial injury has a significant role in COVID-19 pathogenesis. Glycocalyx degradation in SARS-CoV-2 infection causes increased levels of syndecan-1 and Heparan sulfate in the blood which are also markers of organ damage. Therefore, Syndecan-1 and Heparan sulfate are considered important prognostic markers in the morbidity and survival in COVID-19.

6. Limitations

Small sample size.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Abbreviations

RAAS: renin-angiotensin-aldosterone system, ACE2: angiotensin-converting enzyme, Ang-II: angiotensin II, GAGs: glycosaminoglycans, PGs: proteoglycans, ELISA: enzyme-linked immunosorbent assay, SDC-1: Syndecan-1, HS: Heparan sulfate.

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