International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 17s, 2025
https://www.theaspd.com/ijes.php

Can Endothelial Surface Markers Predict Vascular Complications And Hypercoagulability In COVID-19?"

Eman A. Shaheen[1], Hala G. Metwaly[2], Hanan E. Mohamed[1], Dina H. Edrees[1], Manar I Y Ahmed[1]
[1]Clinical and Chemical Pathology Department, Faculty of Medicine, Helwan University, Egypt.
[2] Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, Egypt.

Abstract
The vascular manifestations of COVID-19 have emerged as critical contributors to disease morbidity and mortality, particularly through mechanisms involving endothelial dysfunction and hypercoagulability. In this study, we investigated the predictive value of endothelial surface markers—specifically circulating endothelial cells (CECs) and their progenitors—as indicators of vascular injury and disease severity in COVID-19 patients. Using high-precision flow cytometric analysis, we quantified CECs and endothelial progenitor cells (EPCs) in peripheral blood samples from patients across varying degrees of COVID-19 severity. Our findings demonstrate a statistically significant elevation of both CECs and EPCs in patients with confirmed COVID-19 compared to healthy controls. Moreover, these elevations correlated strongly with clinical markers of hypercoagulability, such as elevated D-dimer levels and thrombotic events, underscoring the central role of endothelial perturbation in the pathophysiology of SARS-CoV-2 infection. Notably, we utilized these endothelial biomarkers to stratify disease severity, revealing their potential as quantitative tools for clinical triage and prognostication. Given the annual recurrence of COVID-19 during winter seasons and its increasingly indistinct clinical profile from other upper respiratory tract infections (URTIs), the need for precise, biomarker-driven diagnostic and prognostic tools has become more urgent. Our study supports the implementation of CEC and EPC profiling as a standardized approach for early vascular assessment in COVID-19, offering a refined lens through which to distinguish and manage cases with potential for severe vascular complications.

Key words: *COVID-19, (SARS-COV-2), circulating endothelial cells, hypercoagulability, Fibrinogen, D Dimer.*

INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization in 2020 (WHO, 2020). The vascular endothelium has emerged as a critical portal of viral entry and a central target in disease pathogenesis. A growing body of evidence implicates endothelial dysfunction as a major driver of the hypercoagulable state characteristic of COVID-19 infection, with thromboembolic complications contributing significantly to the morbidity and mortality of severe cases (Samidurai et al., 2020; Abou-Ismail et al., 2021).

Although SARS-CoV-2 primarily affects the pulmonary system, systemic involvement is common and includes myocardial injury, myocarditis, thromboembolic events, and acute kidney injury. Clinical severity is exacerbated in the elderly and in individuals with underlying comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, and obesity (Yugar-Toledo et al., 2023). Endothelial injury appears to be a central mechanism, mediated both by direct viral invasion and by inflammatory cytokines released during the immune response (Bernard et al., 2020).

The angiotensin-converting enzyme 2 (ACE2) receptor, highly expressed in vascular endothelium, facilitates viral entry into endothelial cells, compromising barrier function and exposing prothrombotic surfaces. This initiates platelet adhesion, activation of the coagulation cascade, and ultimately microvascular and macrovascular thrombosis (Pelle et al., 2022). These mechanisms have emphasized the importance of early vascular assessment in COVID-19, yet routine diagnostic protocols have lacked endothelial-specific markers to predict cardiovascular complications. Several recent studies have advocated the use of novel biomarkers to detect post-infectious endothelial damage, including circulating endothelial cells (CECs) and endothelial progenitor cells (CEPs) (Mancuso et al., 2020; Poyatos et al., 2024; Zhang et al., 2024).

In the present year, 2025, emerging data have reinforced the persistence of hypercoagulable states in COVID-19 patients despite escalated anticoagulation therapy. A multicenter study published in Journal of Clinical Medicine

demonstrated pronounced thrombodynamic activity and elevated thrombin generation parameters in severe COVID-19 cases compared to controls, highlighting the limitations of standard prophylaxis and underscoring the role of endothelial dysfunction in ongoing coagulopathy (PubMed, 2025).

MATERIALS AND METHODS

A. The present study was conducted on sixty adult patients from the isolation units in Kasr Al Ainy hospital and forty control adults that were enrolled from Kasr Al Ainy Hospital, Cairo University. The patients included twenty females and forty males with age range from eighteen to sixty years old.

B. COVID-19 was diagnosed when patients presented with viral pneumonia associated with objective findings on lung-CT scan or chest X-ray, and infection was confirmed by positive SARS-CoV-2 RT-PCR in nasopharyngeal swab, sputum or bronchoalveolar lavage. Patients were hospitalized either in the internal medicine ward or in the intensive care unit (ICU), depending on the severity of their medical condition. Blood samples were collected within 48 hours of patient admission.

C. Selection process was done with simple random selection by taking even patients file numbers. Patients were diagnosed using (reverse transcriptase- polymerase chain reaction) RT-PCR for SARS-COV-2.

D. Inclusion and exclusion criteria were set as follows; inclusion criteria included age group (18-70) and positive RT-PCR for SARS COV 2 while exclusion criteria included cardiac patients **(Boos *et al.*,2006)** and cancer patients, for possible interference with test results regarding endothelial cell markers **(Mancuso *et al.*, 2009)** & **(Guervilly *et al.*, 2020)**.

E. All participants were subjected to the following tests upon admission after recording their medical history; complete blood picture, fibrinogen assessment, D Dimer assessment, (Prothrombin Time) PT and (Partial thromboplastin Time) PTT, flowcytometric assessment of circulating endothelial cells and their progenitors.

E.1. The D Dimer assay combines a two-step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). The Solid Phase Receptacle serves as the solid phase with an anti-FbDP monoclonal antibody adsorbed on its surface as well as the pipetting device. Reagents for the assay are ready-to-use and pre-dispensed in the sealed single-use reagent strips.

E.2. The fibrinogen test depends on the addition of thrombin to fresh citrated plasma. The coagulation time is proportional to the fibrinogen concentration. This allows the estimation of plasma fibrinogen by functional clotting assay.

E.3. The flowcytometric assessment was performed on whole blood samples, which was collected in EDTA tubes. After lysis of blood with ammonium chloride (NH4Cl), cells were incubated with monoclonal antibodies for 15 minutes, at 4 °C, in the dark. CD146 + CECs and CEPs were evaluated by 10-color flow cytometry (Navios EX, Beckman Coulter) using 7-AAD (BD) for viability, and a panel of monoclonal antibodies including anti-CD45 (to exclude hematopoietic cells), anti CD34, anti-CD31 (both from Beckman Coulter), and anti-CD146 (BD) as endothelial cell markers. After acquisition of million events, an appropriate gating strategy was used to enumerate CECs and CEPs (Kaluza software, Beckman Coulter). CECs were identified as CD45−, CD31+, CD34+, and CD146+. CEPs as CD45—, CD31+, CD34+, and CD146–, according to (Mancuso et al, 2020) with modifications. The absolute number of the cells was calculated by a dual platform counting technique using the total number of leukocytes in peripheral blood obtained by hemocytometer, according to routine methods.

STATISTICAL ANALYSIS

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Independent-samples *t*-test of significance, one-way analysis of variance (ANOVA), post Hoc test: Least Significant Difference (LSD), Mann Whitney U test, Kruskall Wallis test, Chi-square (x2) test of significance were used. Confidence interval was set to 95% and margin of error accepted was set to 5%, considering a *P* value < 0.05 to be significant.

RESULTS

Table (1): Comparison between groups according to coagulation test.

Coagulation test	Patients Group (n=60)	Control Group (n=40)	*P*-value
Fibrinogen (g/L)			
Mean±SD	2.69±0.93	2.15±0.34	<0.001**
Range	1.7-6	1.7-3.1	
D DIMER 1 (ng/ml)			
Median (IQR)	800	200	<0.001**
Range	400-11500	100-400	

N.B.: (IQR): Interquartile range, **(Statistics equations used):** Mann-Whitney test for non-parametric data "Median (IQR)" Using: Independent Sample t-test for Mean±SD, *p*-value <0.001 is highly significant.

Table (2): Comparison between patients' groups according to CD 146 negative (CEP) and CD146 positive (CEC).

	Group 1	Group 2	Group 3	Group 4	p-value
CD 146 negative (CEP) (cells/ml)					
Mean ± SD	553.00±0.00	942.30±453.63	1879.36±1208.78	2855.92±1401.56	0.001**
Median (IQR)	553 (553-553) D	866(599-1165) C	1721(928-2436) B	2821(1781-4039) A	
Range	553-553	333-1840	141-5308	540-5308	
CD 146 positive (CEC) (cells/ml)					
Mean ± SD	126.00±0.00	176.00±95.22	335.51±249.40	471.15±298.01	0.002*
Median (IQR)	126 (126-126) D	161(95-229) C	241(171-432) B	420(218-690) A	
Range	126-126	41-399	48-1142	130-1142	

N.B.: (*Group 1*): *Fibrinogen ≤0.4gm/l & D-Dimer ≤0.5 mg/dl), (**Group 2**): Fibrinogen >0.4 gm/L OR D-dimer > 0.5 mg/dl), (**Group 3**): Fibrinogen >0.4gm/l & D-Dimer > 0.5 mg/dl), (**Group 4**): Severe cases (ICU admission/ mortality), (**IQR**): interquartile range, (**Statistical equations used in this test**): Kruskal–Wallis was performed for Median (IQR) & Dunn's test for Multiple comparison Different capital letters indicate significant difference at (p<0.05) among means in the same row, p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.001 is highly significant.*

Table (3): Correlation between CD146 negative (CEP) and CD146 positive (CEC) with parameters of hypercoagulation

Parameters	CD146 negative (CEPs)		CD146 positive (CECs)	
	Rs	*p*-value	Rs	*p*-value
Fibrinogen (g/L)	0.454	<0.001**	0.116	0.377
D DIMER on admission (ng/ml)	0.422	<0.001**	0.558	<0.001**
D DIMER 5th (ng/ml)	0.547	<0.001**	0.517	<0.001**

N.B.: (Statistics equation used): Spearman's rank correlation coefficient (rs), *p*-value >0.05 NS; *p*-value <0.05 S; *p*-value <0.001 HS

Table (4): Correlation between D-Dimer on admission with CD146 negative (CEPs) and CD146 positive (CECs) in groups 2, 3 and 4, using Spearman's rank correlation coefficient (rs).

		D-Dimer on admission		
		Group 2	Group 3	Group 4
CD146 negative (CEPs)	r-value	0.056	-0.223	0.490
	p-value	0.813	0.172	0.089
CD146 positive (CECs)	r-value	0.151	0.156	0.674
	p-value	0.526	0.343	0.012*

N.B.: (Statistical equations used): Spearman's rank correlation coefficient (rs), *p*-value >0.05 is insignificant; **p*-value <0.05 is significant; ***p*-value <0.001 is highly significant

Table (5): Correlation between D-Dimer 5th days with CD146 negative (PECs) and CD146 positive (CECs) in group 2, 3 and 4, using Spearman's rank correlation coefficient (rs).

		D-Dimer 5th day hospitalization		
		Group 2	Group 3	Group 4
CD146 negative (CEPs)	r-value	0.044	0.692	0.526
	p-value	0.853	0.001**	0.065
CD146 positive (CECs)	r-value	0.018	0.518	0.223
	p-value	0.941	0.001**	0.464

N.B.: (Statistical equations used): Spearman's rank correlation coefficient (rs), *p*-value >0.05 is insignificant; **p*-value <0.05 is significant; ***p*-value <0.001 is highly significant

Table (7): Cut- off to discriminate between group 3 & group 4, using CD 146 negative (CEPs) and CD146 positive (CECs).

Items	Cut-off	Sen.	Spe.	PPV	NPV	AUC (C.I.95%)	*p*-value
146 negative PECs	**>2425**	61.5%	74.4%	44.4%	85.3%	0.709 (0.567 to 0.827)	0.017
146 positive CECs	**>295**	69.2%	64.1%	39.1%	86.2%	0.653 (0.508 to 0.779)	0.049

N.B.: (PPV): Positive predictive value which is the ability of the test to predict positive cases, **(NPV):** Negative predictive value which is the ability of the test to predict negative cases, **(AUC (C.I.95%)):** Area under curve with confidence interval 95%.

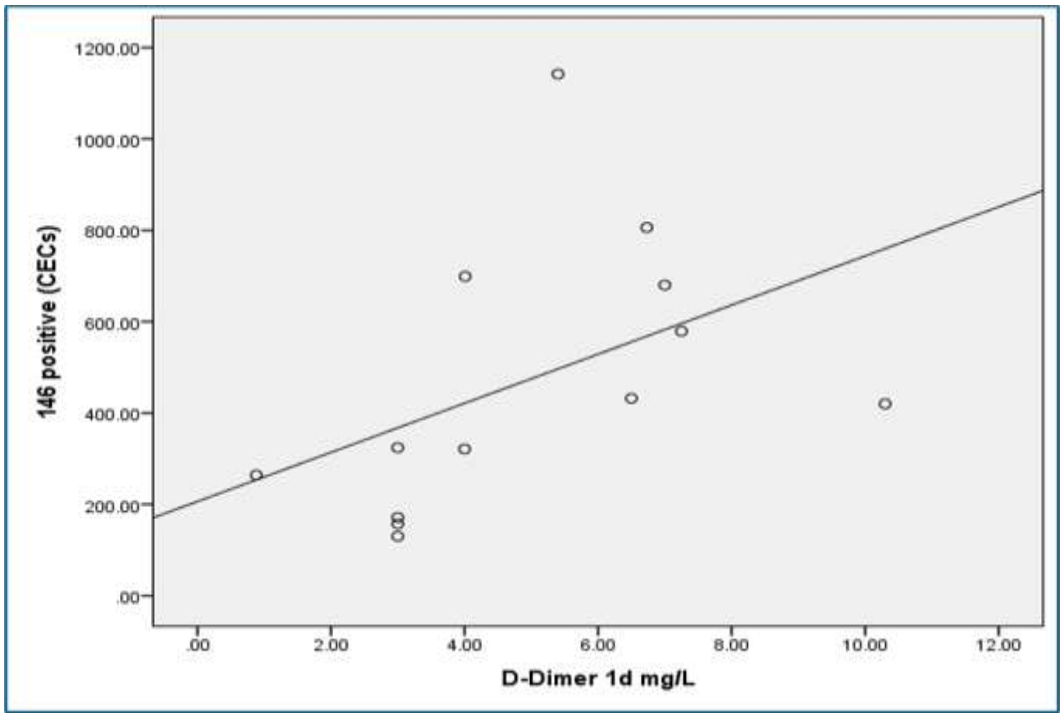

Figure1: scatter blot, showing relation between DDimer on admission and CECs in group3.a CECs

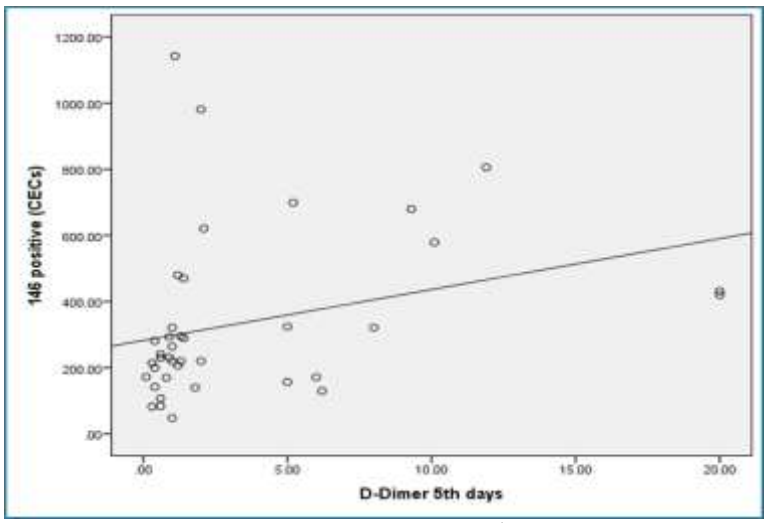

Figure 2: scatter blot, showing relation between DDimer on 5 th day of hospitalization and CECs in group 3positive (CECs) in group 3. plot b

The hypercoagulability state was manifested in COVID-19 patients by high values of both D-dimer and fibrinogen (Table 1). There was a higher ($P < 0.001$) mean value of (fibrinogen) in patients' group than the control group. There was also a higher ($P < 0.001$) median value of (D-dimer on admission) in patients' group than control group. Patients follow up using D Dimer values in 5th day of hospitalization ranged from (0.1-20 ng/ml), Figs 1 & 2.

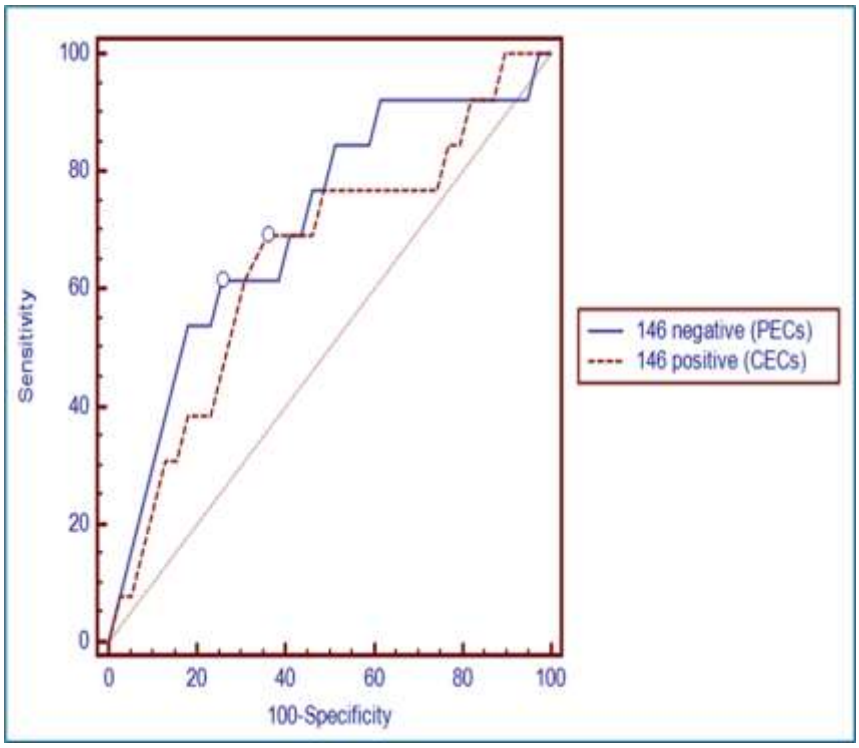

Figure 3: ROC curve showing CECs and CPEs in groups 3 and 4 CECs **CEPs and CECs in groups 3 &**

4. Categorization of disease severity according to flow cytometry analysis

Patients underwent flow cytometry analysis for CD 146 negative CEPs and CD 146 positive CECs to categorize the severity of the disease (Table 2). There was a statistically significant difference between groups according to CD 146

negative (CEP) and CD 146 positive (CEC), Patients in group 1 have normal fibrinogen and D-dimer values, showed CEPs and CECs levels of (553 and 126 cells/mL, respectively). In group 2, patients have elevated levels of both fibrinogen and D-dimer, the levels of CEPs and CECs in this group were as follows (942.3 and 176 cells/mL, respectively). In group 3; patients had high levels of both fibrinogen and D Dimer And the levels for CEPs and CECs were (1879.36 and 335.51 cells/mL, respectively) . Patients in group 4 (Cases who were admitted to ICU and the only case of death) had a mean CEPs of (2855.92 cells/ml) and a mean CECs of (471.15 cells/ml) as shown in figure 3.

Correlation between D-dimer and fibrinogen with CECs and CEPs

The correlation between classic parameters of coagulation (fibrinogen and D Dimer) with parameters proposed in current study (CECs and CEPs) has been determined (Table 3), taking into consideration that D-dimer on the 5th day of hospitalization was performed to assess the development of the disease severity (Table 5). There was a positive correlation ($p < 0.05$) between CD146 negative "CEPs" and CD 146 positive (CECs) with fibrinogen, D-dimer on admission and D-dimer 5th.

There was a significant correlation between values of (CEPs and CECs) with the parameters of hypercoagulability (fibrinogen and D-dimer), yet after categorization of patients according to severity the only significant correlation was proved between D-Dimer on admission and CD146 positive (CECs) in Group 4 (mortality case), with *p*-value (p=0.012). In this table as well, D-dimer at 5TH day of hospitalization showed a significant correlation ($P < 0.001$) with values of CEPs and CECs in group 3 only.

Discrimination between patient group of hypercoagulability state and patient group with severe vascular sequelae

Receiver operating characteristics (ROC) curve was performed for CD146 negative CEPs demonstrated an area under the curve (AUC) of 0.709 (0.567 to 0.827) with *P* value = 0.017. The cut off value for dissemination between group 3 and group 4 was >2425 with sensitivity of 61.5% and specificity 74.4%. Also, the CD146 positive CECs demonstrated an AUC of 0.653 (0.508 to 0.779) with *P* value = 0.049. The cut off value for discrimination between group 3 and group 4 was >295 with sensitivity 69.2% and specificity 64.1%.

DISCUSSION

The resurgence of respiratory viruses post-COVID-19 has complicated differential diagnosis and disease management, especially during seasonal peaks. The epidemiological overlap of SARS-CoV-2 with other viruses such as HMPV, RSV, and influenza has introduced new clinical challenges, particularly in distinguishing severe vascular outcomes unique to COVID-19 (WHO, 2025; CDC, 2025). Among these infections, SARS-CoV-2 continues to demonstrate a distinct pattern of endothelial dysfunction, establishing it as a key differentiator in terms of systemic complications (Libby, 2024; Lim et al., 2024).

Thromboembolic complications remain a major cause of morbidity and mortality in severe COVID-19 cases, and early in the pandemic, D-dimer and fibrinogen were adopted as frontline markers of hypercoagulability. Studies have proposed several cutoff values to stratify disease severity and predict clinical outcomes. D-dimer thresholds ranging from ≥0.5 μg/mL to ≥2 μg/mL have been associated with ICU admission and mortality, with reported sensitivities as high as 92.3% and specificities up to 83.3% (Yu et al., 2020; Poudel et al., 2021; Zhang et al., 2020). Similarly, elevated fibrinogen levels were associated with severe infection, with 528 mg/dL identified as a predictive threshold in previous analyses (Sui et al., 2021; Murat et al., 2021). However, these markers are non-specific and may not fully capture endothelial involvement.

In our study, we incorporated flow cytometric assessment of circulating endothelial cells (CECs) and endothelial progenitor cells (CEPs) as more specific markers of endothelial damage. A statistically significant correlation was observed between these markers and disease severity, hypercoagulability (as measured by D-dimer and fibrinogen), ICU admission, and mortality. Patients were categorized into four groups according to disease severity. The mean CEC levels increased progressively across groups: 126.00 in the normal group, 176.00 in group 2 (either D-dimer

or fibrinogen elevated), 335.51 in group 3 (both elevated), and 471.15 in patients who died in the ICU. Likewise, mean CEP levels were 553.00, 942.30, 1879.36, and 2855.92, respectively.

Our data suggest a stepwise increase in both CECs and CEPs with disease severity, supporting their utility as stratification markers. This aligns with the findings of Guervilly et al. (2022), who reported CEC elevation in critically ill COVID-19 patients, and proposed its use as a non-invasive biomarker of endothelial injury. Conversely, while our study demonstrated elevated CEPs, their correlation with disease severity was less consistent, echoing observations by Mancuso et al. (2020), who found higher CEPs in mild cases but no further increase with severity.

We conducted ROC curve analysis to determine the diagnostic power of CECs and CEPs in distinguishing between severe illness and mortality. A CEC cutoff >295 yielded sensitivity of 69.2% and specificity of 64.1%. For CEPs, a cutoff >2425 provided 61.5% sensitivity and 74.4% specificity. These findings support the inclusion of CECs as reliable indicators of disease progression and adverse vascular outcomes.

Recent studies have also validated these markers. Fernández-Calle et al. (2024) observed persistently elevated CECs in patients with post-acute thrombotic complications, suggesting long-term endothelial damage. In 2025, Weber et al. demonstrated that integrating endothelial biomarkers into clinical scoring models improved prognostic accuracy by 21% for predicting major thrombotic events.

Moreover, our study investigated the dynamic behavior of D-dimer on day 1 and day 5 of admission. A positive correlation was found between D-dimer levels and both CECs and CEPs, particularly in severe and fatal cases. Day 5 D-dimer values >1360 ng/mL were consistent with poor prognosis, as supported by previous reports (Oualim et al., 2020; Reshma et al., 2024).

In conclusion, CECs and CEPs are emerging as sensitive markers for endothelial damage in COVID-19. Their correlation with conventional coagulation markers, disease severity, and mortality underscores their potential clinical value. Incorporating these parameters into diagnostic workflows may improve early risk stratification, inform therapeutic decisions, and enhance outcomes in patients presenting with severe respiratory viral infections, particularly those involving vascular involvement.

STATEMENTS AND DECLARATIONS

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Data Availability

Ethics approval and consent to participate

Written informed consent was obtained from the patients or their relatives.

Consent for publication

Not applicable.

REFERENCES

1. Abate SM, Mantefardo B, Nega S, Chekole YA, Basu B, Ali SA, et al. Global burden of acute myocardial injury associated with COVID-19: a systematic review, meta-analysis, and meta-regression. *Ann Med Surg (Lond)* 2021;68:102594.
2. Abdel-Ghany, M.F., El-Karn, A.F.M., Anis, M.I. *et al.* Study of CRP, ferritin and D-dimer in COVID-19 RICU patients as per HRCT severity in Assiut university hospitals. *Egypt J Bronchol* 18, 87 (2024).https://doi.org/10.1186/s43168-024-00340-8
3. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020 Oct;194:101-115. doi: 10.1016/j.thromres.2020.06.029. Epub 2020 Jun 20. Erratum in: Thromb Res. 2021 Aug;204:146. doi: 10.1016/j.thromres.2020.11.012. PMID: 32788101; PMCID: PMC7305763.

4. Anton MC, Shanthi B, Vasudevan E. Study to Determine a Prognostic Cutoff Values of the Coagulation Analyte D-dimer for ICU Admission among COVID-19 Patients. Indian J Crit Care Med 2023;27(2):135–138.
5. Bernard I, Limonta D, Mahal LK, Hobman TC. Endothelium Infection and Dysregulation by SARS-CoV-2: Evidence and Caveats in COVID-19. Viruses. 2020 Dec 26;13(1):29. doi: 10.3390/v13010029. PMID: 33375371; PMCID: PMC7823949.
6. Bouck EG, Denorme F, Holle LA, Middelton EA, Blair AM, de Laat B, Schiffman JD, Yost CC, Rondina MT, Wolberg AS, Campbell RA. COVID-19 and Sepsis Are Associated With Different Abnormalities in Plasma Procoagulant and Fibrinolytic Activity. Arterioscler Thromb Vasc Biol. 2021 Jan;41(1):401-414. doi: 10.1161/ATVBAHA.120.315338. Epub 2020 Nov 16. PMID: 33196292; PMCID: PMC7942774.
7. Chen CY, Su TC. Benefits and Harms of COVID-19 Vaccines in Cardiovascular Disease: A Comprehensive Review. J Lipid Atheroscler. 2023 May;12(2):119-131. doi: 10.12997/jla.2023.12.2.119. Epub 2023 May 19. PMID: 37265847; PMCID: PMC10232218.
8. Correia RM, Santos BC, Carvalho AAG, Areias LL, Kuramoto DAB, Pereda MR, Aidar ALES, Clezar CNB, Reicher ME, Amorim JE, Flumignan RLG, Nakano LCU. Vascular complications in 305 severely ill patients with COVID-19: a cohort study. Sao Paulo Med J. 2022 Dec 19;141(5):e2022171. doi: 10.1590/1516-3180.2022.0171.R2.17102022. PMID: 36541953; PMCID: PMC10065094.
9. Fish RJ, Neerman-Arbez M. Fibrinogen gene regulation. Thromb Haemost 2012; 108(3): 419–26.
10. Kangro K, Wolberg AS, Flick MJ. Fibrinogen, Fibrin, and Fibrin Degradation Products in COVID-19. Curr Drug Targets. 2022;23(17):1593-1602. doi: 10.2174/1389450123666220826162900. PMID: 36029073; PMCID: PMC10316333.
11. Murat, S., Murat, B., Dural, M., Mert, G. O., & Cavusoglu, Y. (2021). Prognostic Value of D-Dimer/Fibrinogen Ratio on In-Hospital Outcomes of Patients With Heart Failure and Covid-19. *Biomarkers in Medicine*, *15*(16), 1519–1528. https://doi.org/10.2217/bmm-2021-0341
12. Page EM, Ariëns RAS. Mechanisms of thrombosis and cardiovascular complications in COVID-19. Thromb Res. 2021 Apr;200:1-8. doi: 10.1016/j.thromres.2021.01.005. Epub 2021 Jan 18. PMID: 33493983; PMCID: PMC7813504.
13. Paknahad MH, Yancheshmeh FB, Soleimani A. Cardiovascular complications of COVID-19 vaccines: A review of case-report and case-series studies. Heart Lung. 2023 May-Jun;59:173-180. doi: 10.1016/j.hrtlng.2023.02.003. Epub 2023 Feb 8. PMID: 36842342; PMCID: PMC9905103.
14. Parra, L. M., Cantero, M., Morrás, I., Vallejo, A., Diego, I., Jiménez-Tejero, E. (2020). Hospital Readmissions of Discharged Patients with COVID-19. *International Journal of General Medicine*, *13*, 1359–1366. https://doi.org/10.2147/IJGM.S275775
15. Pelle MC, Zaffina I, Lucà S, Forte V, Trapanese V, Melina M, Giofrè F, Arturi F. Endothelial Dysfunction in COVID-19: Potential Mechanisms and Possible Therapeutic Options. Life (Basel). 2022 Oct 14;12(10):1605. doi: 10.3390/life12101605. PMID: 36295042; PMCID: PMC9604693.
16. Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, Maharjan A, Gautam R. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS One. 2021 Aug 26;16(8):e0256744. doi: 10.1371/journal.pone.0256744. PMID: 34437642; PMCID: PMC8389366.
17. Poyatos, P., Luque, N., Sabater, G. *et al.* Endothelial dysfunction and cardiovascular risk in post-COVID-19 patients after 6- and 12-months SARS-CoV-2 infection. *Infection* 52, 1269–1285 (2024). https://doi.org/10.1007/s15010-024-02173-5
18. Saedii, Salah, K., Mikhael, M., Abdulla, N. (2023). 'Value of D-dimer, P-selectin, and fibrinogen as biomarkers for patients with Covid-19', *Minia Journal of Medical Research*, 34(1), pp. 255-264. doi: 10.21608/mjmr.2023.175345.1222
19. Samidurai A, Das A. Cardiovascular Complications Associated with COVID-19 and Potential Therapeutic Strategies. *International Journal of Molecular Sciences*. 2020; 21(18):6790. https://doi.org/10.3390/ijms21186790
20. Samidurai, Arun, and Anindita Das. 2020. "Cardiovascular Complications Associated with COVID-19 and Potential Therapeutic Strategies" *International Journal of Molecular Sciences* 21, no. 18: 6790.
21. Sinha M. Swine flu. J Infect Public Health. 2009;2(4):157-66. doi: 10.1016/j.jiph.2009.08.006. Epub 2009 Nov 7. PMID: 20701877.
22. Sui J, Noubouossie DF, Gandotra S, Cao L. Elevated Plasma Fibrinogen Is Associated with Excessive Inflammation and Disease Severity in COVID-19 Patients. Front Cell Infect Microbiol. 2021 Aug 3;11:734005. doi: 10.3389/fcimb.2021.734005. PMID: 34414135; PMCID: PMC8369350.
23. Vaccination against covid- 19 in Egypt https://covid19.trackvaccines.org/country/egypt/ accessed in 12/2022

24. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020 Nov;195:219-225. doi: 10.1016/j.thromres.2020.07.047. Epub 2020 Jul 27. PMID: 32777639; PMCID: PMC7384402.
25. Yugar-Toledo JC, Yugar LBT, Sedenho-Prado LG, Schreiber R, Moreno H. Pathophysiological effects of SARS-CoV-2 infection on the cardiovascular system and its clinical manifestations-a mini review. Front Cardiovasc Med. 2023 May 16;10:1162837. doi: 10.3389/fcvm.2023.1162837. PMID: 37260945; PMCID: PMC10229057.
26. Yun Yan, Lei Yang, Xiaoli Li, Jian Hao, Bijue Wang, Dan Wang & Junning Wang. (2022) Clinical Characteristics in Patients with Redetected Positive RNA Test After Recovery from Foreign-Imported COVID-19 Cases in Xi'an, China. *Infection and Drug Resistance* 15, pages 3295-3307.
27. Zhang L., Yan X., Fan Q., Liu H., Liu X., Liu Z., Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J. Thromb. Haemost. 2020;18:1324–1329. doi: 10.1111/jth.14859.
28. Zheng R, Zhou J, Song B, Zheng X, Zhong M, Jiang L, Pan C, Zhang W, Xia J, Chen N, Wu W, Zhang D, Xi Y, Lin Z, Pan Y, Liu X, Li S, Xu Y, Li Y, Tan H, Zhong N, Luo X, Sang L. COVID-19-associated coagulopathy: thromboembolism prophylaxis and poor prognosis in ICU. Exp Hematol Oncol. 2021 Feb 1;10(1):6. doi: 10.1186/s40164-021-00202-9. PMID: 33522958; PMCID: PMC7848868.