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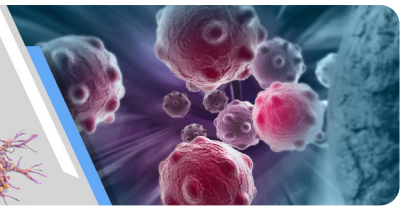

Different Coagulation Markers as Predictors of Severity in Cancer Patients with COVID-19 Infection

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Dear Editor,

The ongoing pandemic of severe acute respiratory syndrome by coronavirus 2 (SARS-CoV-2) has posed several diagnostic and therapeutic challenges for clinicians and researchers around the globe. The first cases were reported from Wuhan, China, in December 2019. The virus rapidly spread worldwide and was declared a pandemic on March 11, 2020 [1]. As of 15th April, 2022more than 500 million cases with more than 6 million deaths have been reported globally due to COVID-19 [2]. Cancer includes a complex set of diseases. The prognosis of all cancers depend on the patient's timely diagnosis, intervention, and overall health status. The COVID-19 pandemic has resulted in some delays in the diagnosis and treatment of cancer patients [3]. In a retrospective cohort study of laboratory-confirmed COVID-19 cancer patients, anti-cancer treatment significantly increased the risk of ICU admission, mechanical ventilation, and death with COVID-19 infection [4]. The in-hospital mortality rates of COVID-19 were 12.1%, 28%, and 45.2% among cancer patients with low, middle, and high viral load, respectively [5]. Due to the increased prevalence of comorbidities and the administration of immunomodulatory drugs, cancer patients are at an increased risk of coagulopathy [6]. The published information on the prognosis of the disease in COVID-19 infected cancer patients and the status of coagulation markers is limited. More studies are needed for prospective long-term follow-up. Numerous studies have reported thrombosis as a common complication for cancer patients. Thrombosis has been identified as the second-leading cause of mortality among cancer patients [7, 8]. Thrombotic complications in cancer patients can range from venous or arterial thromboembolism to disseminated intravascular coagulation [9, 10]. The mechanisms that promote the risk of thromboembolic events in cancer patients appear to be multifaceted and have not yet been completely deciphered [11]. The International Society of Thrombosis and Hemostasis (ISTH) recommends prophylactic administration of anticoagulants in patients for a better prognosis [12, 13]. D-dimer has been extensively researched to predict COVID-19 prognosis with markers of disseminated intravascular coagulation (DIC) [14]. .Billior et al. [15] further reports that the C-reactive protein (CRP) and fibrinogen were better at predicting the disease severity with increased specificity than D-dimer. Among the other implicated coagulation markers, prothrombin fragments 1+2 [15, 16] and thrombin generation assay (TGA) [17-19] have been tested to predict the COVID-19 outcome in severely ill patients. A prospective observational study was designed and conducted at King Faisal Specialist Hospital & Research Center and King Khalid University Hospital from 1st April 2021 to 31st July 2021 to evaluate the different hematological and coagulation markers in admitted patients with confirmed COVID-19 positive patients. In a subgroup analysis of Polymerase chain reaction (PCR) confirmed COVID-19 positive patients with various cancers

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(≥18 years) (n=*38*) with the need for in-hospital treatment were included in this report, all patients had informed consent was obtained from themselves or or their family members. The primary demographic data was collected via the electronic patient chart (CERNER). The prognostic value of the patient's age, gender, D-dimers, prothrombin time/ international normalized ratio (PT/INR), factor VIII (FVIII), thrombin time, fibrinogen (Fib), antithrombin III (ATIII), differential blood cell count and CRP were evaluated for risk of VTE, ICU admission, severe clinical course, and death. The levels of these prognostic biomarkers were measured at hospital admission, ICU admission, intubation, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and death. Our cohort included 38 COVID-19 oncology patients with a female preponderance (55.3%). Risk factors were reported in 97.4% of patients, including hypertension (47.4%), previous VTE (2.6%), hyperlipidemia (10.5%), and other comorbidities in (47.4%) of patients as shown in Table 1. The mean age of our subjects was 58.63±18.61 years, as shown in Table 1. The average length of hospital stay was 13.1 ±10.3 days. At the time of presentation, only 2 of 38 cancer patients presented with basic COVID-19 symptoms, including cough, fever, and shortness of breath. Later, fever developed in 63.2% of patients, with respiratory symptoms in 60.5% and gastrointestinal symptoms in 18.4% of patients. The disease status, rate of thrombosis, and thrombosis prophylaxis have been described in Table 1 for our subjects. VTE prophylaxis was administered to 34 patients: enoxaparin in 27 (79.4%), unfractionated heparin 6 (17.6%) and other in 1 (3.0%). The rate of thrombosis was relatively low for our patients (n=4 ? %). In our subjects, 13 patients were diagnosed with gastric and urogenital cancers, 6 with multiple myeloma and lymphoma, 2 with lymphoblastic leukemia, and 17 with various other types of cancers.

As shown in Table 2, the VTE scores increased from day 1 (5.3 ±2.3) to day-14 (6.7 ±3.7), pointing toward an increased risk of thrombosis over time (p-value = 0.05). INR, PT, and PTT values were initially higher than the normal expected values (1.6 ± 1.7, 17.1 ±4.6, and 41.2 ±10.1, respectively) but gradually reduced during infection (1.1 ± 0.11, 15.2 ± 1.2 and 38.2 ±4.1). Fibrinogen levels similarly increased from day 1 (4.8 ±1.9) to day-3 (4.9 ±1.6), followed by a decrease on day 7 (4.8 ±2.1) and a further decrease on day 14 (4.25 ±2.5). The decrease in fibrinogen levels can be owed to the administration of prophylactic anticoagulants. CRP and creatinine showed a decreasing trend from day 1 (118.3 ±108.5 and 87.8 ±79, respectively) to Day-14 (33.7 ± 69.7 and 72.3 ±44.6, respectively). CRP values were, however, above the normal range throughout the hospital stay, but the correlation was not significant (p-value>0.05). None of the pro-coagulants showed any significant trends (AT: 91 ± 18, PC: 0.9 ± 0.2, PS: 0.7 ± 0.2, vWFAg: 0.8 ±0.1 and FVIII: 0.8 ±0.2). Fib and d-dimer showed interesting patterns. D-dimer values significantly increased from day 1 (1.2 ±1.3) to Day-3 (1.9 ±3.9) and then remained high throughout the hospital stay (p-value<0.001).

On day 14, the cumulative incidence of thrombotic events was 10.52%. Mortality rate in our cohort was 4 out of 38 (10.5%) during study time, with all death occurring within 10 days. The patients who died had different cancers, including multiple myeloma, chest wall tumor, non–small cell lung cancer (NSCLC), and rhabdomyosarcoma. 3 out of the 4 deceased patients had abnormally high VTE scores. D-dimer levels were higher than the normal range in all of these patients, along with other coagulation markers, including fibrinogen. The high mortality rate and increased risk of VTE associated with COVID-19 among cancer patients are

Table 1: Demographic variables and COVID-19 symptom status.

Demographic variable (%age)			
	Males, *n* (%)	**Females, *n* (%)**	
Gender	17 (44.7)	21 (55.3)	
	Mean ± S.D.		
Age *(n =38)*	58.63158 ± 18.60895		
BMI *(n = 38)*	26.81053 ± 7.035808		
Length of Hospitalization *(n = 38)*	13.13158 ± 10.35367		
	Yes	No	
All risk factors	37 (97.4)	1 (2.6)	
Hypertension	18 (47.4)	20 (52.6)	
Bleeding	-	38 (100%)	
Previous VTE	1 (2.6)	37 (97.4)	
Hyperlipidemia	4 (10.5)	34 (89.5)	
Other comorbidities	18 (47.4)	20 (52.6)	
COVID-19 symptoms, *n* (%)			
	Yes	No	
Symptom-free	2 (5.3)	36 (94.7%)	
Fever	24 (63.2)	14 (36.8)	
Respiratory	23 (60.5)	15 (39.5)	
Gastrointestinal symptoms	7 (18.4)	31 (81.6)	
ICU	10 (26.3)	28 (73.7)	
	Thrombosis		
Thrombosis day 0	1 (2.6)	37 (97.4)	
Thrombosis day 3	2 (5.4)	35 (94.6)	
Thrombosis day 14	1 (7.7)	12 (92.3)	
VTE prophylaxis			
	Yes	No	
Patient on VTE prophylaxis	34	3	
	Enoxaparin	Heparin	Other
Type of Prophylaxis	27 (79.4)	6 (17.6)	1 (3.0)

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Table 2: Mean ± Standard deviation values of the coagulation and CBC on days 1, 3, 7, and 14. It also shows the correlation between day 1 and days 3, 7, and 14.

Variable	Mean ± SD (Day 1)	Mean ± SD (Day 3)	p-value	Mean ± SD (Day 7)	p-value	Mean ± SD (Day 14)	p-value
Total VTE score *very low (0-1)* *low (2)* *moderate (3-4)* *high (≥ 5)*	5.3 ± 2.3	5.0 ± 2.0	<0.001	4.8 ± 2.0	<0.001	6.7 ± 3.7	0.05
WBC (4.5 - 11.0 × 10^9/L)	9.2 ± 18.5	8.2 ± 15.6	<0001	7.5 ± 12.0	0.8	6.6 ± 3.5	0.2
Hb (Males: 135 - 175 gm/L) (Females: 120 - 155 gm/L)	118.2 ± 21.1	111.9 ± 22.2	<0.001	112.2 ± 28.2	0.02	113.6 ± 14.3	0.02
Platelet (151x10^3 - 450 x10^3 /mcL)	191.7 ± 100.1	207.0 ± 115.2	<0.001	252.5 ± 155.9	<0.001	251.9 ± 105.3	0.6
NeutAbsolute (1.5 x10^3 - 8.0 x10^3 /mcL)	4.7 ± 3.6	2.9 ± 3.0	<0.001	2.3 ± 1.6	0.01	4.3 ± 2.6	0.8
LymAbsolute (1 x10^3 - 4.8 x10^3 /mcL)	1.9 ± 3.5	1.0 ± .62	0.03	1.2 ± .62	0.008	1.6 ± .6	0.2
MonoAbsolute (0.2 x 10^3 - 0.95 x 10^3 / mcL)	.53 ± .42	0.4 ± 0.2	<0.001	.3 ± .2	0.11	1.4 ± 1.9	0.2
INR (0.8 - 1.1)	1.6 ± 1.7	1.2 ± 0.20	0.02	1.2 ± .15	<0.001	1.1 ± .1	0.6
PT (11 to 13.5 seconds)	17.0 ± 4.9	16.7 ± 2.8	<0.001	16.2 ± 2.0	<0.001	15.2 ± 1.2	.58
PTT (25 – 35 seconds)	41.2 ± 10.1	42.8 ± 7.1	0.07	38.9 ± 4.7	<0.001	38.2 ± 4.0	0.13
D-dimer (<0.50 mg/mL)	1.2 ± 1.3	1.9 ± 3.9	<0.001	1.7 ± 2.1	<0.001	1.9 ± 2.2	<0.001
CRP (<10 mg/mL)	118.3 ± 108.4	80.6 ± 82.9	0.82	40.4 ± 42.9	0.23	33.7 ± 69.7	0.24
Creatinine (Males: 61.9 to 114.9 µmol/L) (Females: 53 to 97.2 µmol/L)	87.7 ± 79.0	80.2 ± 73.6	<0.001	62.6 ± 34.	0.7, <0.001	72.3 ± 44.6	0.8, <0.001
Fib (2.0 to 4.0 g/L)	4.8 ± 1.8	4.9 ± 1.6	<0.001	4.7 ± 2.1	0.003	4.2 ± 2.5	0.56

in line with previous reports [20]. Racial and ethnicity-based disparities have been observed in the prognosis of COVID-19 and the associated mortality rates among cancer patients [21, 22]. This suggests that racial and ethnic differences might lead to varying pathogenic pathways and immune responses across the globe. The observations of this study delineate the importance of D-dimer, Fib, INR, PT, PTT, and CRP in the prognosis of COVID-19 among Saudi cancer patients. Fibrinogen and thrombin are essential coagulation biomarkers for ICU admission or death in COVID-19 patients [15]. D-dimer and PT have been reportedly increased in patients [23-25]. CRP has been established as a predictor of the COVID-19 disease course [26]. However, no study has investigated these coagulation markers among COVID-19 infected cancer patients. These markers can guide the clinical management [27] of the disease and prioritize healthcare resources [28]. The cancer patients have already suffered from decreased allocation of healthcare resources than warranted since the start of the pandemic [3]. These findings can help guide the prophylactic administration of anticoagulant therapy for cancer patients and reduce the in-hospital mortality rates. In conclusion, high D-dimer, INR, PT, PTT, Fib, and CRP values at admission point toward an increased risk of thrombotic events, ICU admission, and a high mortality rate. The administration of prophylactic agents in the patients may reduce the risk of thrombosis and ICU admission, increasing the overall life expectancy.

References

1. Organization WH. Naming the coronavirus disease (COVID-19) and the virus that causes it. Brazilian Journal of Implantology and Health Sciences 2 (2020).
2. WHO. WHO Coronavirus (COVID-19) Dashboard (2022).
3. Li Y, Wang X, Wang W. The Impact of COVID-19 on Cancer. Infection and Drug Resistance 14 (2021): 3809.
4. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Annals of oncology 31 (2020): 894-901.
5. Westblade LF, Brar G, Pinheiro LC, et al. SARS-CoV-2 viral load predicts mortality in patients with and without cancer who are hospitalized with COVID-19. Cancer cell 38 (2020): 661-71. e2.
6. Gervaso L, Dave H, Khorana AA. Venous and arterial thromboembolism in patients with cancer: JACC: CardioOncology state-of-the-art review. JACC: CardioOncology 3 (2021): 173-190.

7. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. The lancet oncology 6 (2005): 401-410.
8. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. British journal of cancer 102 (2010): S2-S9.
9. Levi M. Cancer-related coagulopathies. Thromb Res 133 (2014): S70-5.
10. Eichinger S. Cancer associated thrombosis: risk factors and outcomes. Thromb Res 140 (2016): S12-7.
11. Falanga A, Marchetti M, Russo L. The mechanisms of cancer-associated thrombosis. Thromb Res 135 (2015): S8-s11.
12. McDonald B, Davis RP, Kim SJ, et al. Platelets and neutrophil extracellular traps collaborate to promote intravascular coagulation during sepsis in mice. Blood, The Journal of the American Society of Hematology 129 (2017): 1357-1367.
13. de Stoppelaar SF, van't Veer C, van der Poll T. The role of platelets in sepsis. Thrombosis and haemostasis 112 (2014): 666-677.
14. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis 18 (2020): 844-8447.
15. Billoir P, Alexandre K, Duflot T, et al. Investigation of Coagulation Biomarkers to Assess Clinical Deterioration in SARS-CoV-2 Infection. Frontiers in Medicine 8 (2021).
16. Al-Samkari H, Song F, Van Cott EM, et al. Evaluation of the prothrombin fragment 1.2 in patients with coronavirus disease 2019 (COVID-19). American journal of hematology 95 (2020): 1479-1485.
17. Billoir P, Duflot T, Fresel M, et al. Thrombin generation profile in non-thrombotic factor V Leiden carriers. Journal of thrombosis and thrombolysis 47 (2019): 473-477.
18. Billoir P, Miranda S, Damian L, et al. Development of a thrombin generation test in cultured endothelial cells: Evaluation of the prothrombotic effects of antiphospholipid antibodies. Thrombosis research 169 (2018): 87-92.
19. Miranda S, Billoir P, Damian L, et al. Hydroxychloroquine reverses the prothrombotic state in a mouse model of antiphospholipid syndrome: role of reduced inflammation and endothelial dysfunction. PLoS One 14 (2019): e0212614.
20. Patell R, Bogue T, Bindal P, et al. Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19. Journal of Thrombosis and Haemostasis 18 (2020): 2349-2357.
21. Kopel J, Perisetti A, Roghani A, et al. Racial and gender-based differences in COVID-19. Frontiers in public health 8 (2020): 418.
22. Bibbins-Domingo K. This time must be different: disparities during the COVID-19 pandemic. American College of Physicians (2020): 233-234.
23. Lippi G, Favaloro EJ. D-dimer is associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. Thromb Haemost 120 (2020): 876-878.
24. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 323 (2020): 1061-1069.
25. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18 (2020): 844-847.
26. Rauch A, Labreuche J, Lassalle F, et al. Coagulation biomarkers are independent predictors of increased oxygen requirements in COVID-19. Journal of Thrombosis and Haemostasis 18 (2020): 2942-2953.
27. Quintana-Díaz M, Andrés-Esteban EM, Ramírez-Cervantes KL, et al. Coagulation Parameters: An Efficient Measure for Predicting the Prognosis and Clinical Management of Patients with COVID-19. Journal of Clinical Medicine 9 (2020): 3482.
28. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. bmj (2020): 369.