Contributions of age, race, and anticoagulant Protein S in prediction COVID-19 prognosis

Taylor Collins & Rinku Majumder, PhD.

Louisiana State University Health Sciences Center, Department of Biochemistry and Molecular Biology, New Orleans, LA.

Introduction

❖COVID-19 patients experience hypercoagulability and increased risk of venous thromboembolism. Severe cases of COVID-19, i.e., patients who require ventilators, are associated with hyper-coagulability and disseminated intravascular coagulation (DIC). Moreover, several reports indicate that hypercoagulability, as measured by the D-Dimer level, is present mostly in critically ill and deceased patients. In addition to blood clots of all sizes throughout the body, doctors who treat coronavirus patients report a range of other odd and frightening syndromes, such as kidney failure, cardiac inflammation, and immune complications. Most severely ill COVID-19 patients manifest a hyperactivated immune response, led by interleukin 6 (IL6) that triggers a so called “cytokine storm” and hyper coagulopathy. Hypoxia is also associated with COVID-19.

❖Deficiency of the anticoagulant protein, Protein S, is associated with DIC and thrombosis. Protein S limits thrombin generation by directly inhibiting Factor IXa. Thus, the high thrombotic risk associated with PS deficiency is due to failure to regulate thrombin formation.

❖D Dimer levels, age, and race, can affect the severity of COVID-19 and the degree of mortality. Clinicians measure the D dimer levels as an indicator of hypercoagulability and DIC. A positive D-dimer result indicates the presence of an abnormally high level of fibrin degradation products; thus, high D dimer suggests substantial blood clot (thrombus) formation and consequent degradation. The elderly are more susceptible to contracting COVID-19, and they have a higher risk of mortality compared with younger individuals. In addition, people of African and Hispanic origin are also at higher risk of infection.

Methods

The purpose of this research was to identify factors that can predict the risk of severe COVID-19 and its prognosis. We found that age, race, and the plasma level of anticoagulant Protein S comprise a list of risk factors that lead to severity and mortality of COVID-19. However, experimental data are required to directly correlate Protein S level with severity of COVID-19 disease.

In order to collect data, we examined previously published research papers in order to compile statistics that determine parameters for establishing specific values of how age, race, and D dimer levels can predict specific COVID-19 outcomes.

Hypothesis

★We speculate that hypoxia plus IL6-driven cytokine explosion causes a severe drop in Protein S level and exacerbates the thrombotic risk in COVID-19 patients.

★Here we highlight a mechanism by which the IL6-hypoxia curse causes a deadly hypercoagulable state in COVID-19 patients, and we suggest a potential therapeutic path to treatment (Figure 1).

Results

Table 1: Correlation Between Age and Mortality in COVID-19

Place	Time and Date	No of patient	Sex		Age	Mortality
			Male	Female		
Netherlands[1]	7th March - 5th April, 2020	184	139	45	Average : 64	23
Lombardy region of Italy[2]	20th February -18th March, 2020	1591	1304	287	Median : 63	405
Italy[3]	Until 15th March, 2020	22512	13462	9050	Median : 64	1625
Zhongnan Hospital of Wuhan University in Wuhan, China[4]	1st January to 13th March, 2020	449	268	181	Average : 65.1	134
Fatal Cases of COVID-19 from Wuhan China[5]	9th January-15th February, 2020	85	62	23	Median: 65.8	All
Wuhan Jin Yin-tan Hospital, Wuhan, China[6]	Late December, 2019-26th January, 2020	52	36	17	Average: 59.7	32

Table 2: Studies which indicate that hypercoagulability (supra-physiological levels of D-dimer), is almost always associated with disease severity and mortality in COVID-19.

Study	Sample size	Mean D-dimer (<0.5 µg/ml)	p-values	Comment
Tang et al, Feb 2020,[7]	Survivors (162)	0.6	<0.001	Disseminated intravascular coagulation (DIC) was found in most deaths
	Non-survivors (21)	2.12		
Han et al, Mar 2020, [8]	Ordinary patient (49)	2.14 ±2.88	<0.001	Huge increase in D-dimer in critically ill COVID patients
	Critical (10)	20.04 ± 32.39	<0.05	
Wang et al, Mar 2020, [9]	ICU (36)	4.14	<0.001	In the non-survivors, D-dimer increased continuously
	Non-ICU (102)	1.66		
Zhang et al, April 2020, [10]	Ordinary (276)	0.41	<0.001	12 non-survivors had D-dimer values greater than 2.0
	Severe (67)	4.76		
Spiezia et al, April 2020, [11]	ICU (22)	5.343 ±2.099	<0.0001	All ICU patients with acute respiratory failure showed severe hypercoagulability, one patient with the most hypercoagulable state died.
Ranucci et al, April 2020, [12]	Total (16)	3.5	0.017	Seven patients died of hypoxia and multi-organ failure
Tang et al, May 2020, [13]	Survivors (315)	1.47	<0.001	30 of the non survivors died even after treated with low molecular weight heparin
	Non-survivors (134)	4.7		

Results

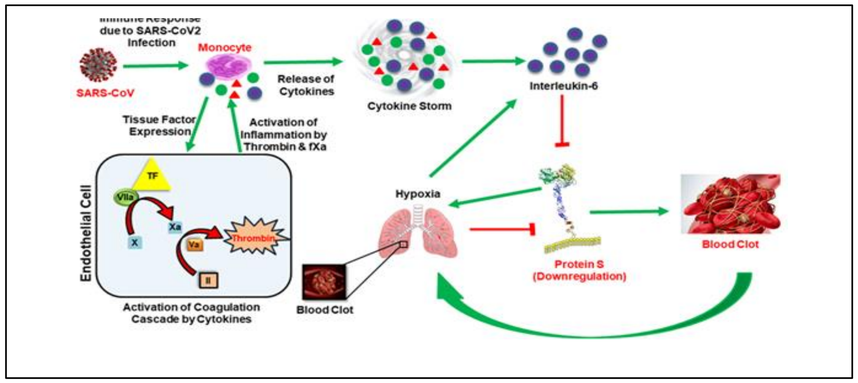

Figure 1: In the presence of the SAR-COV2 virus, early response proinflammatory cytokines (IL-6, TNFα, IL-1β etc.) are induced and activate the coagulation cascade by stimulating tissue factor (TF) expression from monocytes. The presentation of tissue factor leads to the formation of thrombin by the TF-VIIa pathway. Thrombin produces clots, and clots get wedged into arteries in the lungs and cause thrombotic complications and hypoxia. Hypoxia also induces IL-6. Simultaneously, thrombin augments inflammation and accelerates the production of proinflammatory cytokines, termed ‘cytokine storm’. Both cytokine storm and hypoxia downregulate Protein S, leading to coagulopathy.

Discussion

Literature search showed that mortality rate is higher in older population (Table 1) and hypercoagulability is associated with disease severity and mortality in COVID-19 (Table 2).

It was shown before in a population of stroke patients, IL6 was upregulated, and it caused downregulation of Protein S that resulted in venous thrombosis(14). Our work demonstrated that hypoxia downregulates Protein S synthesis in HepG2 cells (15) . Further, we showed that Protein S supplementation in thrombotic mice (mimicking hypoxic niche) plasma was able to alleviate the thrombotic risk (15). Thus, we propose that Protein S supplementation could be useful in treating thrombotic complications. A substantial number of severe COVID-19 patients manifest both hypoxia and prothrombotic complications and we speculate that reduced Protein S level might play a key role in the disease progression of these patients.

References

1. Klok FA, Kruip M. van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV and Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020.
2. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS -CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020.
3. Livingston E and Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA. 2020.
4. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. J Am Coll Cardiol. 2020.
5. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P, Li T, Cao F, Chang C, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. Am J Respir Crit Care Med. 2020.
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5):475-481.
7. Tang N, Li D, Wang X and Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18(4):844-847.
8. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH and Zhu CL. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020.
9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020.
10. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z and Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020.
11. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P and Simioni P. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thromb Haemost. 2020.
12. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, Falco M, Albano G and Menicanti L. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020.
13. Tang N, Bai H, Chen X, Gong J, Li D and Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18(5):1094-1099.
14. Vila N, Reverter JC, Yague J and Chamorro A. Interaction between interleukin-6 and the natural anticoagulant system in acute stroke. J Interferon Cytokine Res. 2000; 20(3):325-329.
15. Pilli VS, Datta A, Afreen S, Catalano D, Szabo G and Majumder R. Hypoxia downregulates protein S expression. Blood. 2018; 132(4):452-455.

This research project was supported by grant # 1659752 through the National Science Foundation (NSF) and NIAAA (K99/R00 AA022651), Research Experiences for Undergraduates (REU) Program