International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Role of Von Willebrand Factor in COVID-19: Literature Review

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Abstract: ***Corona virus disease can directly infect endothelial cells characterized by signs and symptoms of endothelial damage. Circulating biomarkers of endothelium is useful to manage COVID patients. This review highlights the role of von Willebrand factor in COVID.***

Keywords: COVID-19, Biomarkers, von willebrand factor

1. Introduction

COVID-19 is caused by SARS-CoV-2 infection. Although this infection has been shown to affect the respiratory system, a high incidence of thrombotic events has been observed in severe cases of COVID-19 and in a significant portion of COVID-19 nonsurvivors.

Endothelial cell injury has been a primary finding in autopsies of COVID-19 non survivors and may contribute significantly to the procoagulant state observed in these patients. Corona virus disease can directly infect endothelial cells characterized by signs and symptoms of endothelial dysfunction. Circulating biomarkers of endothelium are useful to diagnose and manage COVID-19patients. The following review highlights the role of von Willebrand Factor level in COVID-19.

2. Literature Studies

George Goshua et al., studied 68 COVID-19 patients with elevatedvon Willebrand Factor antigen levels in ICU patients 565% (SD 199) compared to other non ICU hospitalized patients 278% (SD 133) with p <0.0001 [1].

A study of 243 COVID-19 adults showed increased von Willebrand Factorantigen [2].

Eleni E. Ladikou et al. reported biomarkers in 24 COVID-19 patients admitted in the ICU with mortality 25%and elevated von Willebrand Factor antigen levels 350 (302-433). von Willebrand Factor levels were high in patients who did not survive (median 477%) compared to those who survived (335%) with p =0.015 [3].

Vineeth Thomas et al. conducted a study with 143 COVID-19 patients and found that von Willebrand Factor level independently correlated with COVID-19 severity and death [4].

Douglas D Fraser et al studied endothelial cell injury markers in COVID-19 patients and found that von Willebrand Factor was significantly elevated in COVID-19 ICU patients compared to that of healthy controls [5]

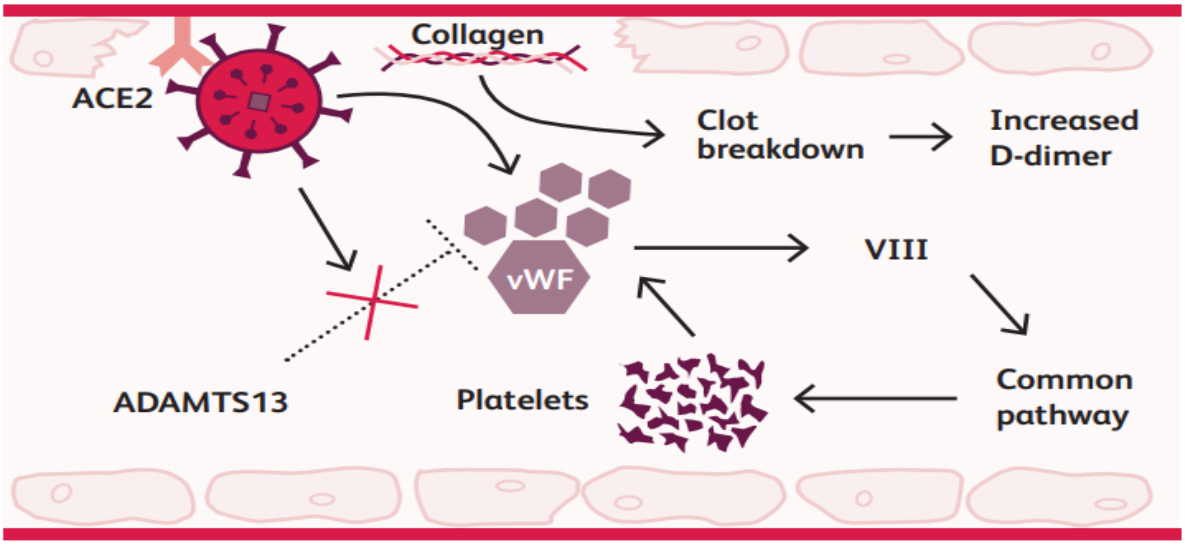
Table 1: Studies of vWFin COVID-19 patients

Author	Sample size	Age (Median)	M/F	Marker	Endpoint	
					ICU	Death
Goshua	68	62	27/41	vWF Ag ↑	20	_
Rauch	243	63.9	155/88	vWF Ag ↑	41	10
Ladikou	24	65	18/6	vWF Ag ↑	19	4
Thomas	143	54	104/39	vWF Ag ↑	-	23
Fraser	10	61	3 /7	vWF Ag ↑	10	-

3. Discussion

Von Willebrand Factor (VWF) is a glycoprotein actively involved in platelet adhesion and aggregation. Willebrand Factor (VWF) is synthesized and stored in megakaryocytes, vascular endothelial cells (ECs) and platelets. von Willebrand Factor endothelial expression is characterized by circulating von Willebrand Factor. von Willebrand Factor plays role in primary as well as secondary hemostasis. In Primary hemostasis, the process of the platelet clot formation at the site of blood vessel injury takes place. For proper primary hemostasis to occur, platelet adhesion and aggregation must occur. During platelet adhesion at the site of blood vessel injury, platelets can bind directly to the exposed subendothelial collagen (via GPIa-IIa or GPVI receptors) or indirectly via von Willebrand Factor. von Willebrand Factoralso performs an important role in secondary hemostasis. Secondary hemostasis involves coagulation factors and the coagulation cascade to produce a fibrin meshwork at the site of vessel injury. von Willebrand Factor facilitates the secondary hemostasis process in two ways. First, von Willebrand Factor serves as a carrier protein for Factor VIII, extending Factor VIII's half-life in the plasma. Although this may initially seem trivial, the von Willebrand Factor carrier activity stabilizes Factor VIII and significantly extends its half-life 4 to 6-fold. Second, it releases and concentrates Factor VIII at the site of injury. Factor VIII is a clotting

factor that, when activated, complexes with other factors to ultimately produce fibrin. To highlight the significance of von Willebrand Factor in this process, mutations affecting the von Willebrand Factor binding site for Factor VIII leads to decreased levels of Factor VIII, known as Type 2N von Willebrand disease (vWD), resulting in a clinical presentation similar to hemophilia A, which is a bleeding disorder that occurs when an individual lacks the ability to produce adequate amounts of Factor VIII for proper clotting. There is strong evidence from the literature that the SARS-CoV-2 infection causes endothelial cell injury, likely due to an indirect mechanism. The ULVWF released from injured endothelium likely causes an imbalance of the VWF: ADAMTS13 ratio, leading to thrombosis and platelet activation. Therefore, endothelial injury and dysfunction account, at least partially, for the coagulopathy and hypercoagulability observed in patients with COVID-19. Targeting the VWF/ADAMTS13 axis may provide a new strategy to reduce COVID-19 systemic complications [6].



Marked von Willebrand Factor levels in COVID-19 patients is due to the virus entering the cells via the transmembrane protein ACE2. ACE2 is expressed on the surface of alveolar epithelial cells, and arterial and venous endothelial cells. The virus enters into the cell causes to inflammation and endothelial cells damage causing release of von Willebrand Factor.

4. Conclusion

This review summarizes evidence of endothelial dysfunction caused by coronaviruses. There was an increase in the von Willebrand Factor antigen levels in COVID-19 patients, and the highest levels of von Willebrand Factor antigen were found in deceased COVID-19 patients. von Willebrand Factor antigen-biomarker of endothelial dysfunction significantly associated with an increased composite poor outcome in patients with COVID-19.

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