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Evaluation of Von Willbrand factor antigen level in severely affected Covid 19 patients

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Abstract
Background: Severely affected COVID-19 cases with respiratory rate > 30 cycle/minute, pneumonia features and oxygen saturation < 90% may have high VWF due to endothelial cell damage.
Aims of the study: Evaluation of Von Willbrand Factors antigen levels. Finding correlations among (VWF), D dimer and oxygen saturation.
Methods: This cross sectional study was conducted on 50 PCR positive patients were severely affected and admitted to hospitals (Al-Imamain Kadhimian medical city, IBN AL-Khateeb hospital and Dar Al Salam 1field hospital) from January till May 2021. The leftover of plasma samples anticoagulated with trisodium citrate were used for evaluation of VWF: Ag by VIDAS system using VWF kit with ELFA technique. Other parameters were taken from patients files.
Results: The study included 33 males and 17 females with age range of (34-86) years. Mean of VWF, D dimer were high. Oxygen saturation was significantly low and inversely correlated with VWF. There were statistically significant correlations (P Value < 0.05) between VWF and D dimer.
Conclusions: Von Willbrand Factor level was elevated in all patient SD, elevated VWF correlated with elevated D dimer and inversely with oxygen saturation.

Key words: Evaluation, Von Willbrand, factor, severely, COVID-19

Introduction

VWF is synthesized in endothelial cells and megakaryocytes, it is stored within the α-granules of the platelets and Weibel-Palade bodies of endothelial cells. The ultra-large, high molecular weight multimer are involved in hemostasis, platelet adhesion and play a critical role in the pathogenesis underlying micro vascular occlusion in several conditions including thrombotic thrombocytopenic purpura (TTP), cerebral malaria and COVID-19 infection [1-3], plasma von Willebrand factor (VWF) levels are significantly increased in patients with COVID-19 as it is an acute phase protein that increases in response to acute infection, inflammation and endothelial cell injury that result in pouring of high amounts of VWF stored in wieble pallade bodies of these cells [2]. Interestingly however, the elevated plasma VWF: Ag levels in severe COVID-19 could be due to a decreased VWF clearance by its cleaving metalloprotease enzyme ADAMTS 13. Acquired deficiency of that enzyme is associated also with systemic disorders, including severe inflammatory diseases and sepsis [4, 5]. Considering that COVID-19 is a severe inflammatory disease, it is logical that it is associated with acquired ADAMTS-13 deficiency and, hence, increased levels of high molecular weight ultra large VWF multimeres [6-8]. Han *et al* conducted a case control study in which they examined hemostatic parameters from 94 SARS-CoV-2-infected patients. The differences were more prominent in D-dimer between the two groups (10.36 vs. 0.26 ng/L; P < 0.001). Notably, the increase in D-dimer value was more significant in severely affected and critically ill patients [9]. Guan *et al*. performed an analysis on 1099 patients and reported D-dimer levels of more than 0.5 ng/L was seen in 260/560(46.4%) cases. Forty-three percent of the non-severe patients showed raised D-dimer, whereas the incidence was about 60% in severely affected patients [10]. Other studies showed that plasma VWF: Ag levels increased significantly during ICU stay, peaking at a median of 690.2 (467-848.4) IU/dl. Thus, VWF levels measured during each time period were significantly higher compared to the previous measurements [2]. Helms *et al*. has published a multicenter prospective cohort study in France, assessing thrombotic risk in COVID-19 patients admitted to ICU and ventilated, which showed that VWF and factor VIII were considerably increased and decreased level of oxygen saturation [11].

In comparison with it, other study enrolled by Eleni E.*et al*. revealed high levels of VWF in patients with severe infection who were not ventilated and no statistically significant differences between ventilated (Critically Ill) and non-ventilated (severely affected) COVID-19 patients with low oxygen saturation [12].

Aims of the stud

Evaluation of Von Willbrand Factors antigen levels. Finding correlations among (VWF), D dimer and oxygen saturation.

Methods

This descriptive cross sectional study was conducted on 50 PCR positive patients from Al-Imamain Kadhimian medical city, IBN AL-Khateeb hospital and Dar Salam 1 hospital who were severely affected by COVID-19 infection and admitted to hospital depending on the WHO criteria for classification of COVID-19 patients.

Inclusion criteria

1. Patients over 15 years of age.
2. Hospitalized COVID-19 patients who are severely affected.
3. Newly admitted patients.
4. Tested positive for SARS-cov2 by PCR.

Exclusion criteria

1. Critically ill patients who were admitted to intensive care unit due to prolonged period of illness and multiple interventions.
2. Patients with known current or previous history of deep venous thrombosis, pulmonary embolism, prosthetic heart valve, anticoagulant therapy as heparin or enoxaparin.

Materials

Plasma sample anticoagulated with trisodium citrate, vidas VWF kit, mini vidas system Blood sample anticoagulated with trisodium citrate centrifuged at 3000 rpm for 15min. to obtain platelet rich plasma that is applied to the VWF strip to be analyzed by mini vidas system depending on spectrophotometry at 450nm to detect the level of VWF in patients' samples. D dimer levels and oxygen saturations were taken from their files.

Results

1. Age and gender distribution

The age range was (34-86) years. The mean was 55.62 year±11.77 years SD. The study group included 33 males and 17 females i.e. 66% and 34% respectively and the M:F ratio was 2:1. The mean age and SD for male and female subgroups were 58.61±11.927 years and 49.82±9.255 years respectively as illustrated in Figure1.

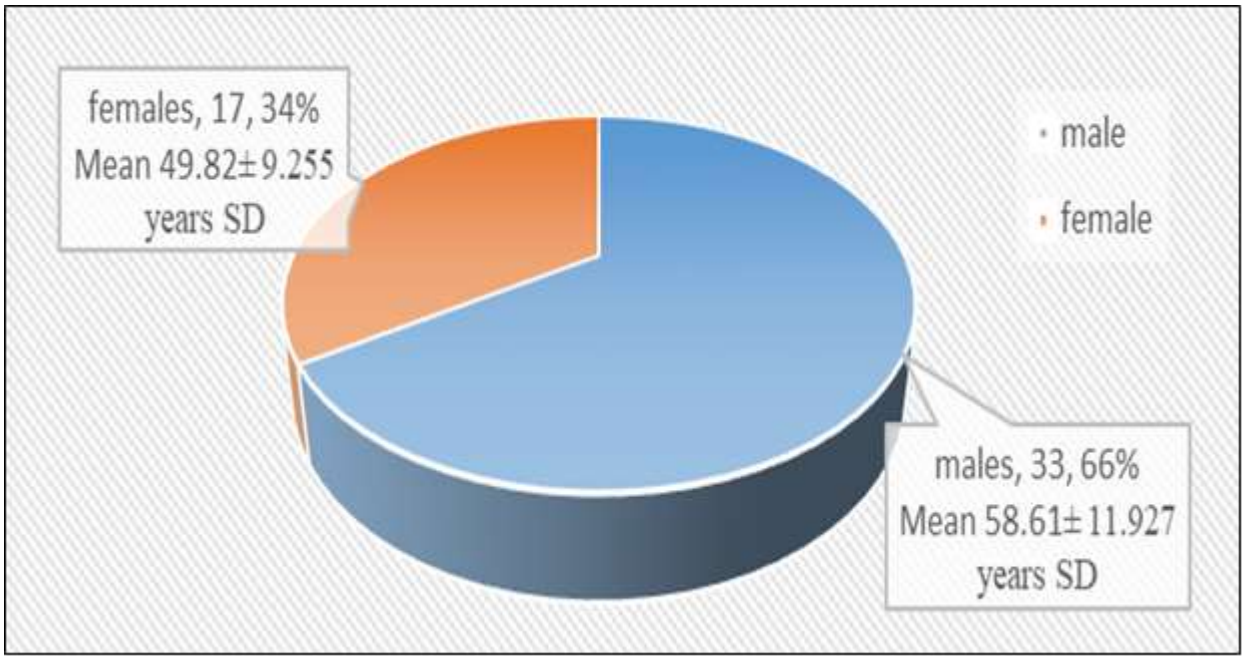

Fig 1: Frequency and percentages of patients by gender and age

2. Range, mean and standard deviation of age, gender, VWF, D-dimer and oxygen saturation in the study

Table 1: There was an inverse relationship between oxygen saturation and the level of VWF as illustrated

Statistics	Age (year)	D-Dimer µg/ml	O2 Saturation %	VWF I.U/dl or %
Range	34-86	1.3-19.7	76-90	241.5-924
Mean ± SD	55.62±11.770	6.738±4.5378	85.74±3.4629	516.499±223.2487
Total No of Patients	50			

Oxygen saturation percentage

The oxygen saturation range was (76%-90%) with a mean of 85.74%± 3.46 as shown in Table 1 There was an inverse relationship between oxygen saturation and the level of VWF as illustrated in Figure 2 and statistically significant.

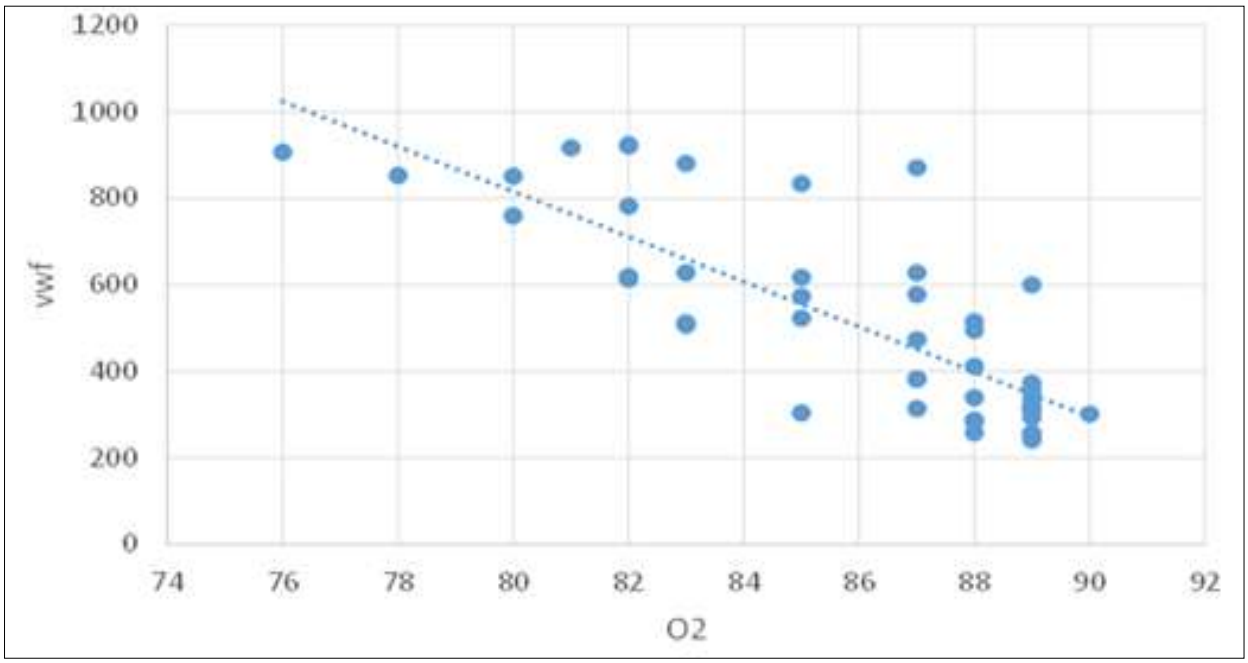

Fig 2: Show statistically significant

The correlations between VWF: Ag, D dimer and oxygen saturation: There was a proportional relationship between VWF and D dimer while an inverse relationship between VWF and oxygen saturation (p value < 0.05).

Table 2: Show Variables and R (correlation coefficient)

Variables	R (correlation coefficient)	P Value
D dimer µg/mL	0.860	0.000
O2 saturation%	-0.807	0.000

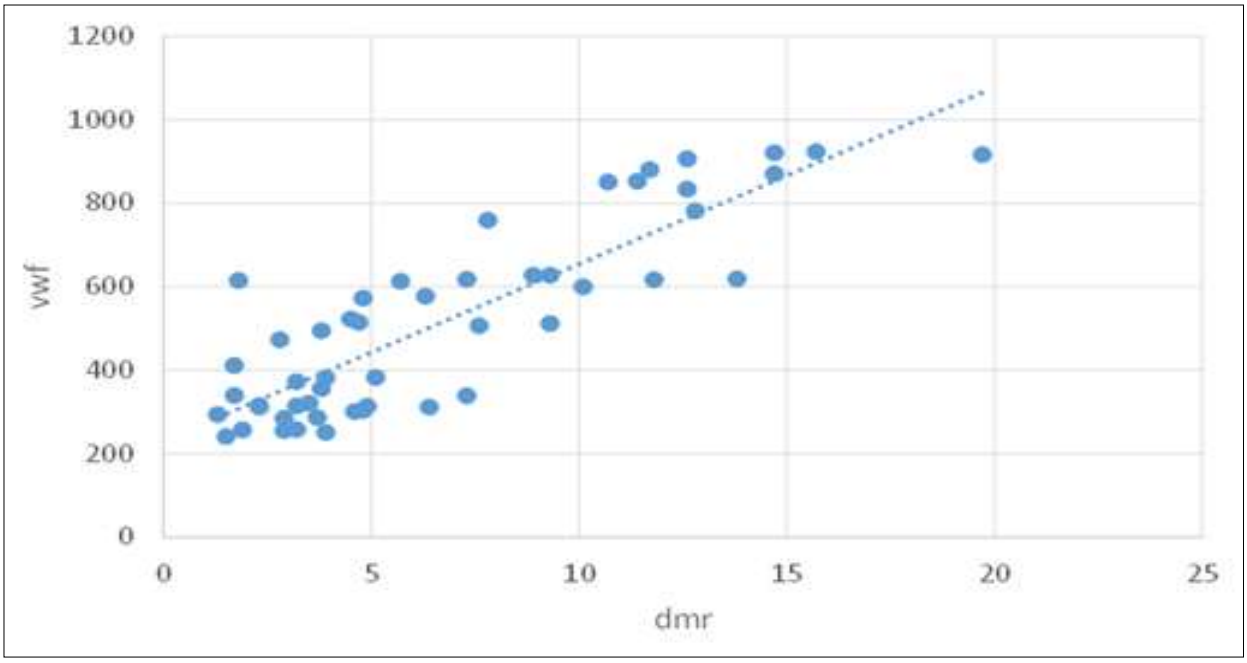

Fig 3: Show Direct relationship between VWF and D dimer

Discussion

This cross sectional study included 50 PCR positive severely affected patients with COVID-19 infection who were selected sequentially from Al-Imamain Kadimain medical city, IBN Al-khateeb hospital and Dar Al-Salam hospital over a period of time from January till May 2021 after taking in considerations the inclusion and exclusion criteria. The main concern of this study was to evaluate the level of VWF: Ag in those severely affected patients which was typically high in all of them with a range from 241.5% to 924% as a highest level obtained. It was not a surprise to obtain such high values of VWF: Ag in these cases as VWF is both an acute phase reactant that increase in response to acute inflammation/ infection and that what happens in respiratory tract inflammation induced by the virus. Besides it is stored in endothelial cells of respiratory tract that are

severely damaged by the virus with subsequent release of large amounts of VWF especially the ultra large high molecular weight multimers. Moreover high level of cytokines as IL-1, TNF, IL-6 that inhibit ADAMTS13 protease resulting in higher levels of VWF that can be detected in the plasma of these patients. This result was consistent with that of Nuccia Morici *et al* and Bernardo *et al*. [13-15]. The high levels of VWF correlate well in a statistically significant proportional relation with the high levels of D dimer as all patients were severely affected with severe inflammatory response leading to the elevated levels of VWF. Moreover those patients were prone to microthrombi formation due to endothelial cell injury through activation of coagulation cascade and fibrinolytic system with high D dimer levels (16). Such findings were consistent with the findings of Antoine Rauch *et al* (4) in his study that revealed elevated level of VWF and D dimers at admission which were associated with severe infection thus they conclude that both parameters could be considered as vital independent diagnostic and prognostic markers and could be used as predictors for the higher need for oxygen therapy irrespective of age, gender and other comorbidities. A statistically significant inverse relations were found between the mean levels of VWF and oxygen saturation i.e. the higher levels of VWF are associated with low level of O2 saturation. Such findings were consistent with the findings of Antoine Rauch *et al* [4] in his study that revealed elevated level of VWF and D dimers at admission which were associated with severe infection thus they conclude that both parameters could be considered as vital independent diagnostic and prognostic markers and could be used as predictors for the higher need for oxygen therapy irrespective of age, gender and other comorbidities [17].

Conclusion

Von Willbrand Factor level was highly elevated in all severely affected COVID-19 patients and its level was closely related to the low oxygen saturation percentage thus it could be considered as a marker to assess the severity of the infection. Elevated VWF correlates well with elevated D dimer that enable it to be used as a marker for following up those patients. High level of VWF was mostly associated with low platelet count supporting the possibility of micro thrombi formation in those patients. Expand research on hemostatic complications by increasing sample size, tracking VWF levels, and evaluating additional diagnostic and prognostic markers such as factor VIII, fibrinogen, interleukins, and ADAMTS 13.

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