Clinical Analysis of Relationship between Clot Formation in Covid-19 Patients and Factor Ⅶ Level by Case Control Study in Holly Karbala City

Jullanar Z. Daeweesh[1], A-S. U. Hassan[2]
[1, 2]Department of, Pathological Analysis, College of Health and Medical Techniques /Kufa, Al-Furat Al-Awsat Technical University, Iraq
Email: jullanar.darweesh.chhu11@student.atu.edu.iq

ABSTRACT
Objective: Coagulopathy is one of dangerous symptoms found in critically ill coronavirus patients (COVID-19). Factor VII (proconvertin) is one of coagulation factors that involve in coagulation cascade, although their relevance in COVID-19 is uncertain. The goal of this study was to determine the prevalence and factorVII in COVID-19 patients Method: There were 80 patients admitted to the hospital. 40 of them were positive for COVID-19 infection by RT- PCR, whereas the other 40 were healthy controls. FVII levels were measured in both groups. Result: all patient showed higher levels FVII level in patients group (415.92±102.76) then in control group (341.72±33.54) conclusion: COVID-19 patients showed relatively elevated levels of FVII than healthy individuals this is probably gave a nearby clew to explain the process of thrombus formation.
Keywords: Covid-19, Fvii,Thrombosis

1. Introduction

Coronaviruses are spherical, enveloped, single-stranded, positive-sense RNA viruses. Named for the ultra-structural "crown-like" (corona) appearance of the spike proteins on the virion surface. They can cause intestinal, respiratory, neurologic, or systemic disease syndromes [1]. Contact with body fluids such mucous membranes (eyes, nose, and mouth) or respiratory droplets causes it (nasal drip, coughing, or sneezing) [2]. Increased body temperature, myalgia or weariness, and a dry cough are the most common symptoms of COVID-19. Within one week after the commencement of sickness, patients with severe disease may develop dyspnea and hypoxemia. Acute respiratory distress syndrome (ARDS) or end-organ failure may develop quickly [3, 4].
Co-thromboplastin was a clotting factor of the human coagulation system. It was a vitamin K-dependent protein that was mad exclusively by the liver. Plasma levels range around 0.35 to 0.60 mg/L. Its half-life is extremely short (4-6 hours). The glycoprotein human coagulation factor VII (FVII) has a molecular mass of 50 KDa. It is produced in the liver and circulates in the blood at a concentration of 0.5g/ml in the plasma. Tissue factor (TF), an integral membrane protein that serves as a cellular receptor, activates FVII [5].
Coagulation factor VII (FVII) is the key triggering enzyme of the extrinsic coagulation pathway. Tissue factor (TF) is an integral membrane protein that is widely expressed in normal and cancerous tissues. Coagulopathy may play a role in COVID-19 pathogenesis [6].

2. Method

40 COVID-19 patients were attended to Al-hayat unit of alhussein medical city –Iraq,and 40 healthy control. the patients were positively diagnosed by RT-PCR
Exclusion criteria: COVID -19 Patients on previous anticoagulant Treatment.
All patients were undergoes multiple investigations including lab tests.physical exam,radiological examination, ultrasound, RT-PCR,
The patients where already received antiviral drugs along with anti-fever medication with no previous anticoagulant administration.This study was approved by the Ethics Committee of AL-Hussein Medical City - Iraq
The laboratory diagnosis was done by the following:CBC by automated hematology analyzer system of Sysmex \Japan,D-dimer and ferritin by MONARCH 300 chemistry analyzer \Fortress diagnosis –UK,aPL by Biotek ELISA system

3. Statistical Analysis

Data were showed as means ± standard deviation (SD), T test, Chi secure test. test were used to analyze the differences between the two groups (case and control), P-value <.05 was defined as statistically significant. Statistical analysis was Performed by using SPSS software

4. Result

Both male and female groups were effected by COVID-19 infection with all ages. In terms of biomarkers and biochemical indicators, there was a substantial difference between patients suffered from COVID-19 infection and control group. study

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was showed non-significant correlation between FVII and biomarkers except for platelets.

Table (1) comparison of FVII levels according to demographic characteristics of patients and patient with COVID-19 infection and healthy controls

variable	group	N	Mean	Std. Deviation	T-test	P-value
groups	Patients	40	415.92	102.76	4.341	0.000*
	controls	40	341.72	33.544		
Age class	<=65 y patients	18	401.79	105.584	-2.781	0.040*
	> 65 y patient	22	427.48	101.366		
gender	Male patients	24	414.60	94.91	-0.981	0.099
	Female patients	16	417.90	116.76		
*at α0≥0.05						

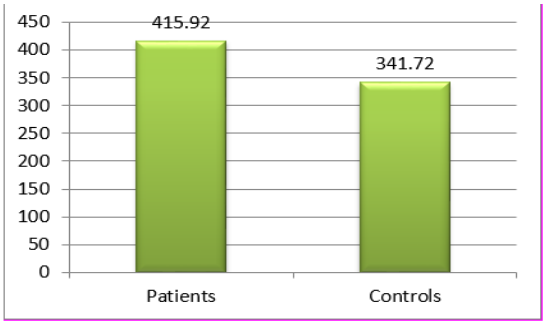

Figure (1) graphical comparison of proconvertin mean level of COVID-19 patients and controls

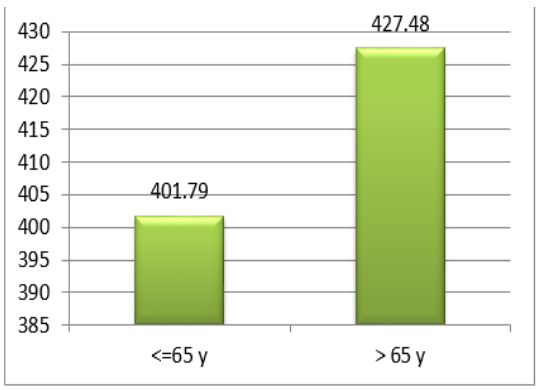

Figure (2) graphical comparison of proconvertin mean level of COVID-19 patients age groups

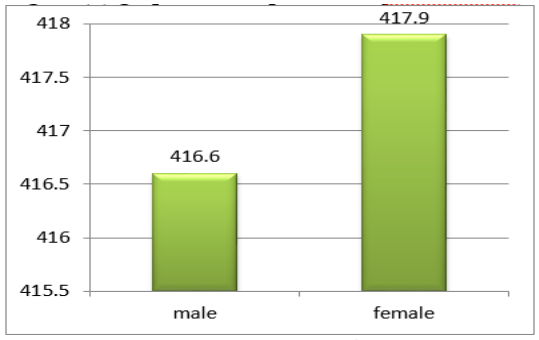

Figure (3) graphical comparison of proconvertin mean level of COVID-19 patients gender groups

Table (2) correlation coefficient of Factor Ⅶ and parameters among COVID-19 infection.

parameters	Correlation coeffeciant	p-value
FVII & d-dimer	0.309	0.052
FVII & ferritin	0.007	0.968
FVII & CRP	0.090	0.580
FVII & WBC	0.073	0.656
FVII & platelets	0.336	0.034*
FVII & apl	0.222	0.169
** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).		

5. Discussion

As shown in table (1) and figure (1) the factor FVII level was higher in patients group (415.92±102.76) then in control group (341.72±33.54)

Severe sepsis was nearly always linked to systemic coagulation activation. There was plenty of data demonstrating a broad cross-talk between hemostasis and inflammation, which is likely to be involved in the pathophysiology of organ failure in sepsis patients.,The most important initiator of thrombin formation in sepsis was tissue factor. Studies of experimental or human endotoxemia or cytokinemia have demonstrated a central role of the tissue factor/factor VIIa system in the initiation of thrombin initiation [7].

As shown in table (1) and figure (2) the factor FVII level was lower in patients >65 y (401.79±105.584) then in <=65 y patients (427.48±101.366)

In healthy people, blood coagulation capability increased with age, owing to a rise in plasma concentrations of major procoagulant agents. This phenomenon might play a part in the rise in cardiovascular disease and thrombosis that comes with becoming older. Furthermore, at the time of weaning, blood coagulation capacity in humans and other animals reached a young adult level, followed by a gradual rise during young adulthood and an almost 2-fold increase by old age [8, 9].

according to survival models Of Patients with decreased levels of these coagulation proteins had an increased risk of death [10].

As shown in table (1) and figure (3) the factor FVII level was nearly the same in male patients (414.60±94.91) then in female patients (417.90±116.76)

In earlier ages, women had considerably lower mean levels of FVIIc and FVIIa than males, but at older ages, the opposite was true. Postmenopausal women exhibited considerably higher mean levels of FVIIc and FVIIa after age adjustment than premenopausal women. Hormone replacement treatment considerably reduced the rise in FVIIc in postmenopausal women, and a similar trend was found in FVIIa. High FVIIc levels were related with oral contraceptive usage, and this impact was mostly due to an increase in FVII:Ag [11].

According to table (2) the findings showed a week direct association (r=0.309) existed between factor VII (pg/ml) and d-dimer(mg/ml) that was statistically

significant at (p-value=0.052).
There was association between clustering of the vitamin K-dependent factors (prothrombin, VII, IX, X) and FXI and FXII. high levels of coagulation factor (F)VIII,FIX and FXI in turn reported as association with an increased risk of venous thrombosis [12].
According to table (2) the findings showed a week direct association (r=0.007) existed between factor Ⅶ (pg/ml) and ferritin (mg/ml) that was statistically significant at (p-value=0.968).
Owing high levels of iron might be both beneficial and detrimental to cardiovascular health, it might reduce the risk of clogged arteries, also, it might raise the risk of blood clots caused by reduced blood flow.
According to table (2) the findings showed a week direct association (r=0.090) existed between factor VII (pg/ml) and CRP (mg/ml) that was statistically significant at (p-value=0.58)
The inflammation and DVT are closely linked, at which increased level of plasma CRP might serve as be a predictor of DVT. Increased plasma levels of Fg (fibrinogen), FVIII and FIX all were also important risk factors to DVT. The interaction between inflammation and coagulation promotes the occurrence of DVT. which may be one of DVT pathogenesis [13].
According to table (2) the findings showed a week direct association (r=0.073) existed between factor Ⅶ (pg/ml) and WBC (*10^9/ml) that was statistically significant at (p-value=0.656)
Leukocytes may operate as a predectoer for tissue factor expression and produce proinflammatory and procoagulant molecules such as granular enzymes, cytokines, and damage-associated molecular patterns, among other things. As a result, these mediators may have an impact on all aspects of thrombus formation, such as platelet activation and adhesion, as well as activation of the intrinsic and extrinsic coagulation pathways [14].
According to table (2) the findings showed a week direct association (r=0.336) existed between factor Ⅶ (pg/ml) and platelets (*10^9/ml) that was statistically significant at (p-value=0.034*)
Platelets partsipated their hemostatic capacity by adhesion, activation and aggregation, which were triggered by tissue injury, and these actions stimulate the coagulation factors and other mediators in order to achieve hemostasis [15].
According to table (2) the findings showed a week direct association (r=0.222) existed between aPL (U/mg) and factor Ⅶ (pg/ml) that was statistically significant at (p-value=0.169)
It was hypothesized that aPL promoted thrombosis via stimulating the expression of TF in blood arteries and blood cells. The key initiator of in vivo coagulation was Tissue Factor. The TF/FVIIa complex then acts as an activator for FIX and FX, resulting in the production of thrombin and fibrin. FVIIa is a weak serine protease on its own, but its catalytic activity is enhanced when it binds TF 2 × 10*7fold [16].

6. Conclusion

This study revealed that serum level of FVII is correlated with platelets count in patients with COVID-19 infection.
There is significant difference could be seen in FVII level between patient and control groups and between age groups, but no significant difference could be seen between male and female. this study fairly showed that COVID-10 infection would cause elevated levels of serum FVII which may help in exeplination of COVID-related thrombosis formation.

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8. Nomenclature

Abbreviation	Meaning
COVID-19	Coronavirus disease -2019
FVII	factor VII
RT-PCR	real time-polymerase chain reaction
ARDS	acute respiratory distress syndrome
Mg\l	milligram\litter
Kda	killodalton
TF	tissue factor
CBC	complete blood count
SD	standard deviation
FVIIc	Factor VII Coagulant Activity
FVIIa	Activated Factor VII
FVIIAg	factor VII antigen
DVT	deep vein thrombosis
Fg	fibrenogene

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