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The Impact of COVID-19 on Blood Coagulation Profile among Sudanese Hospitalized Adult Patients

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Abstract

Covid-19 is a severe acute respiratory syndrome, the disease presents with a ranging from asymptomatic to severe symptomatic illness with multiple organ failure and death, and can cause a severe effect on the coagulation system. This study aimed to determine the effect of the covid 19 on the extrinsic and intrinsic pathway of coagulation [prothrombin time(PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT)] and to determine the association of age and gender with the severity of COVID-19 in Sudan in order to improve the outcome. A cross-sectional study carried out among 487 COVID-19 patients attending Khartoum State. COVID-19 patients were confirmed by RT-PCR. For all patients, the prothrombin times (PT), International normalized ratio (INR), and Activated partial thromboplastin (APTT) were estimated by using a semi-automated coagulometer analyzer. Patients were divided into three subclass groups according to the Severity of COVID-19 (mild, severe in the emergency room (ER) and intensive care unit (ICU), and the clotting factors values were compared between the groups. The results were statically analyzed by spss version 21 for data analysis. These results showed statistically significant increased Levels of PT, INR, and APTT for all (P. value = 0.000), compared to the control group. Also, the levels of coagulation tests were higher in ICU COVID-19 patients (P. value = 0.000) compared to mild and severe subgroups. This study concluded that: coagulation clotting times were increased in COVID-19 patients, especially among patients in ICU which could be a marker for DIC and even death.

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Introduction

The Coronaviruses is severing acute respiratory syndrome (Lu *et al*., 2020) emerged in Wuhan (China) at the end of 2019 with an unknown cause (Di Gennaro *et al*., 2020), in January 2020, after a few weeks later, take a sample from the lower respiratory tract for analysis, identified a novel virus severe acute respiratory syndrome coronavirus as a causative agent for that observed pneumonia cluster (Huang *et al*., 2020). the disease named SARS-CoV-2 "COVID-19" by Dr. Tedros Adhanom Ghebreyesus, in 2020 (March 11th) when there was an increased number of countries involved (114), with more than 118,000 cases and over 4000 deaths, then the WHO declared the pandemic status (Llitjos *et al*., 2020). The disease ranges from asymptomatic to severe symptomatic illness with multi-organ failure and death (World Health Organization Director-General's Opening Remarks at the Media Briefing on COVID-19–11, 2020). Respiratory droplet transmission is the main route and it can also be transmitted through asymptomatic carriers by person-to-person contacts (Abou-Ismail *et al*., 2020). COVID -19 can cause severe effects on coagulation systems. The complication of coagulation activation can be leading to the formation of disseminated intravascular coagulation (DIC) and death (Lupia *et al*., 2020). The systemic inflammatory response by COVID -19 can cause severe effects in coagulation systems leading to endothelial damage, coagulation activation, and intravascular fibrin deposition (Yang *et al*., 2020). the complication of coagulation activation can be leading to the formation of thrombus and even disseminated intravascular coagulation (DIC) (Qiu *et al*., 2020). The coagulation blood cascade is start when the sub-endothelial tissue factor is exposed to the blood flow followed either by activation or damage of the endothelium. It may happen as a result of the activation of endothelium or perforation of the vessel wall by cytokines, chemicals, or inflammatory processes by extrinsic pathway (PT and INR) and extrinsic pathway (APTT) (Bikdeli *et al*., 2020).

Materials and Methods

This was a cross-sectional study, conducted among 487 COVID-19 patients. Information about gender, age, COVID -19 symptoms, Ethical permission was taken from Ethical Research Committee, faculty of Medical Laboratory Sciences, Alzim Alazhari University, certainly an informed consent was taken from selected

subject before participation in the study The primary data was gathered using a self-administered questionnaire; this was particularly designed to obtain data that would support in the study. The isolation hospitals use a real-time polymerase chain reaction device AccuPower® COVID-19 RT-PCR kit to confirm the diagnosis of COVID-19 patients (Bioneer Corporation, Daejeon, South Korea) following the manufacturer guidance; all cases were positive for COVID-19 by RT-PCR. PT, INR, and APTT clot analysis were performed for patients and 302 healthy individuals as a control group using Stago semi-automated analyzer. Patients were further subdivided into three subgroups [77 mild COVID-19,137 severe COVID -19 (ER) and 273 patients in ICU], subject-categorized according to the following: the first group with or without clinical evidence of pneumonia but without oxygen requirements ("mild" group), the second group with oxygen requirements ("severe" group (ER) and the last group under mechanical ventilation (ICU group). The study was approved by the University of Alzaeim Alazhari committee.

Statistical Data Analysis

Statistical analysis was performed by Statistical Package for Social the Sciences (SPSS software version 16) for windows. P. values equal or less than 0.05 was considered statistically significant.

Results and Discussion

This cross-sectional study was carried out on 487 COVID-19 patients (304 males and 183 females), aged between 20-88 years old in Sudan hospitals in Khartoum State during the period from April 2020 to December 2020. PT, INR, and APTT results were statically analyzed by SPSS version 21 to obtain descriptive statistics (mean (±) SD, minimum and maximum results) also one-way ANOVA test was used for the comparison of more than two parameters, and an independent T-test used to compare between two parameters to obtain the P-value (P-value less than 0.05 was considered significant). These results showed statistically significant increased Levels of PT, INR, and APTT among patients with COVID-19 when compared with the control (for all P-value = 0.000) **Table 1**. Also, the levels of coagulation tests were higher in ICU COVID-19 patients compared to mild and severe subgroups **Table 2**. No statistical significant was revealed between PT, APTT, and INR among mild Covid-19 patients and control group (p value 0.987, 0.990, 0.137) respectively. Data were summarized in **Table 3**.

In this study (56% of a patient admitted into the ICU unit, 28.1% were admitted to ER unit, and 15.8% of covid 19 patients with mild symptoms), male was more affected by the disease than female; 303 versus 184, respectively. Also, males were mainly represented in the ICU unit (male 183 (67.3%) versus female 90 (32.7%) **Table 5**. This study showed that ages up to 60 years (97.5%) with COVID-19 and mainly represented in the ICU unit **Table 4**.

Table 1. Comparison of PT, APTT, and INR between Covid-19 patients and control group

Variables	Case (n=487)	Control (n=302)	P value
PT	15.2	13.9	0.000
INR	1.21	1.08	0.000
APTT	47.9	33.2	0.000

Mann-Whitney test was used to calculate the P-value
A p-value less than 0.05 is considered significant

Table 2. Comparison of PT, APTT, and INR between Covid-19 patients' subgroups and control group

Variables	ICU (n=273)	Sever (ER) (n=137)	Mild (n=77)	Control (n=302)	*P value	** Multiple P values
PT	19.6	14.3	13.9	13.9	0.000	AXB 0.000 AXC 0.000 AXD 0.000 BXC 0.005 BXD 0.000 CXD 0.869
INR	1.53	1.13	1.08	1.08	0.000	AXB 0.000 AXC 0.000 AXD 0.000 BXC 0.000 BXD 0.000 CXD 0.957
APTT	60	44.7	30.7	33.2	0.000	AXB 0.000 AXC 0.000 AXD 0.000 BXC 0.000 BXD 0.000 CXD 0.000

* Kruskal Wallis Test was used to calculate the P-value
** Mann-Whitney test was used to calculate the P-value
A p-value less than 0.05 is considered significant

Table 3. Comparison of PT, APTT, and INR between mild Covid-19 patients and control group

Variables	Mild(n=77)	Control (n=302)	P-value
PT	13.684±1.0223	13.705±1.0027	0.987
INR	1.063±.1550	1.065±.1546	0.990
APTT	30.807±2.838	33.532±4.087	0.137

Table 4. Distribution of age groups among COVID-19 subgroups

Study groups		COVID-19 Subgroup			Total
		ICU	Mild	Sever (ER)	
Age groups	20-40	5 (5.8%)	72 (84.7%)	8 (9.4%)	85
	41-60	72 (35.8%)	3 (1.4%)	126(62.6%)	201
	More than 60	196 (97.5%)	2 (0.99%)	3 (1.4%)	201
Total		273 (56%)	77(15.8%)	137 (28.1%)	487

Table 5. Distribution of gender among COVID-19 subgroup

Study groups		COVID-19 Subgroup			Total
		ICU	Mild	Sever (ER)	
Gender	Female	90 (48.9%)	49 (26.6%)	45 (24.4%)	184
	Male	183 (60.3%)	28 (9.2%)	92 (30.3%)	303

Total	273 (56%)	77 (15.8%)	137 (28.1)	487

Recently the whole world affected by the pandemic COVID-19 which become rapidly spreading, and dangerous and may lead to death especially for the old aged, also with time there is wide heterogeneity regarding clinical remark for the disease, due to the virus diversity. The dangerous COVID-19 complications are to induce severe acute respiratory distress syndrome and multiple organ failure (MOF), which are at risk of DIC and death (Chang, 2019). Mortality of the covid 19 seems to be relatively low among patients with the critical disease or at high risk of developing acute respiratory distress syndrome and being admitted to ICU (Han *et al*., 2020). This study was conducted to determine the effect of COVID-19 on the extrinsic and intrinsic pathway of coagulation (PT, INR, and APTT) and to determine the severity of COVID-19 in Sudan regarding age and gender in order to improve the outcome. This study showed that significantly increased in PT, INR, and APTT among covid-19 patients when compared to control groups (P Value 0.000).

As mentioned in previous studies, COVID -19 can lead to disturbance in coagulation systems. The most dangerous outcome is the activation of coagulation which can be leading to the formation of disseminated intravascular coagulation (DIC) and death (Lupia *et al*., 2020). PT and APTT are simple and first-line investigations for patients with coagulation disturbance and their results can predict the occurrence of DIC.

This study showed that there was no significant difference in PT, INR, and APTT results between patients in ER (severe) and mild subgroups (P.value < 0.05) but it was highly significantly increased among ICU patients (p.value 0.000). This current study agreed with the (Yongwei *et al*., 2020) report that significantly increased PT, INR, and APTT among patients with COVID-19 than healthy controls (p-value <0.05) (Sayad & Rahimi, 2020) and agreed with (Sayad & Rahimi, 2020) showed statistically significant in PT, INR and APTT result in ICU patient [pv<0.05] (Jin *et al*., 2020) also this study was in concordance with (You *et al*., 2020) showed a significant increase in PT (P.value 0.000, INR (P.value 0.000) in COVID-19 patient (Luo *et al*., 2020), but This study was disagreed with (Micco *et al*., 2020), showed statistically insignificant in PT, INR, and APTT (P.value > 0.05), this variation may relate to the low sample size of their study (67 patient). This recent study included (303) males and (184) females (56% of a patient admitted to the ICU unit, 28.1% were admitted to ER unit, and 15.8% of covid 19 patients with mild symptoms), this study revealed that males are more affected (60.3%) than female (48.9%) mainly represented in ICU unit, this study was similar to (Mahajan & Kaushal, 2020); the incidence in male =76%, and female =46% (Mahajan & Kaushal, 2020). This study showed that aged up to 60 years (97.5%) are more likely to get COVID-19 and represented in the ICU unit, the study was in agreement with (Pastor-Barriuso *et al.*, 2020); demonstrated that the old age individuals up to 60 years more likely to get COVID-19 infection with more complicated symptoms.

Conclusion

This study concluded that significant increase in PT, INR, and APTT in covid 19 patients, especially among ICU covid 19 subgroups compared to mild and severe subgroups, which may indicate a risk of bleeding and or thrombosis that could lead to death (Adiga, 2019). Old age is more likely to increase the severity of covid 19 infection (Abd Elwahaab *et al*., 2019).

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