بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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Estimation of the prognostic value of plasma ADAMTS-13 in covid-19 patients

Thesis

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List of Abbreviations

ACE	Angiotensin converting-enzyme
ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AFOP	Acute fibrinous and organizing pneumonia
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ARDS	Adult respiratory distress syndrome
ASH	American Society of Hematology
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
CBC	Complete blood count
CCL	C-C motif chemokine ligand
CD	Cluster differentiation
CORADS	The coronavirus disease 2019 (COVID-19) Reporting and Data System
CoV	Coronavirus
COVID-19	Coronavirus disease of 2019
CPAP	Continuous positive airway pressure
CQ	Chloroquine
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CXCL	Chemokine (C-X-C motif) ligand
DAD	Diffuse alveolar damage
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
DOACs	Direct oral anticoagulants
ELISA	Enzyme-linked immunosorbent assay
FDA	Food & Drug Administration
FDP	Fibrin degradation products
FiO2	Fraction of inspired oxygen
GBS	Guillain-Barré Syndrome

GGO	Ground-glass opacity
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony stimulating factor
GP	Glycoprotein
HCoV-NL63	Human coronavirus NL63
HFNO	High flow nasal oxygen
Hg	Hemoglobin
HIV	Human immunodeficiency virus
HLH	Haemophagocytic lymphohistiocytosis
HRCT	High-resolution computed tomography
HUS	Hemolytic uremic syndrome
ICU	Intensive Care Unit
IL	Interleukin
IMV	Invasive mechanical ventilation
INF	Interferon
INR	International normalized ratio
IP-10	Interferon-Inducible Protein 10
ISTH	International Society on Thrombosis and Haemostasis
JAK	Janus kinase
LDH	Lactate dehydrogenase
LMWH	Low-molecular-weight heparin
MERS	Middle East respiratory syndrome coronavirus
mRNA	messenger ribonucleic acid
MSOF	Multisystem Organ Failure
NP	Nasopharyngeal
PEEP	Positive end expiratory pressure
PHEIC	Public Health Emergency of International Concern
PLT	Platelets
P-SILI	Patient self-inflicted lung injury
PT	Prothrombin time
RDRP	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
RR	Respiratory rate

RT-PCR	Reverse transcriptase polymerase chain reaction
SARS	Severe acute respiratory syndrome
SD	Standard deviation
sHLH	Secondary or acquired haemophagocytic lymphohistiocytosis
TCZ	Tocilizumab
TGF-β	Transforming growth factor beta
TLC	Total leucocytic count
TMAs	Thrombotic microangiopathies
TNF	Tumour necrosis factor
TPE	Therapeutic Plasma Exchange
TTP	Thrombotic thrombocytopenic purpura
UFH	Unfractionated heparin
UL-vWF	UL- vWF ultra-large von Willebrand factor
VKAs	Vitamin K Antagonists
VTE	Venous thromboembolism
vWF	von Willebrand factor
WHO	World Health Organization

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Introduction

Von Willebrand factor (vWF), a glycoprotein critical for supporting platelet adhesion and aggregation at sites of vessel injury, exists in the plasma as a series of multimers**.** The platelet-tethering function of von Willebrand factor (VWF) is proteolytically regulated by ADAMTS13) a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) which cleaves the Tyr1605-Met1606 (P1-P1′) bond in the VWF A2 domain **(*Xiang et al., 2011*).**

ADAMTS13 deficiency allows unchecked thrombus growth to cause microangiopathic hemolysis, thrombocytopenia, and tissue infarction. At present, ADAMTS13 deficiency with a high-titer inhibitor level appears to be associated with an increased risk of early death and subsequent relapse. If ADAMTS13 is absent, VWF-dependent platelet accumulation continues, eventually causing microvascular thrombosis and TTP ***(Plautz et al., 2018)***.

The decreased activity of ADAMTS13 can be seen not only in TTP, but also in metastatic malignancy or after surgery. It has been reported that a complete lack of ADAMTS13 in mice results in a prothrombotic phenotype. In addition, the decreased activity of ADAMTS13 in patients with acute systemic inflammation suggests a relationship between inflammation and ADAMTS13 deficiency **(*Kedar et al., 2018*).**

Coronavirus disease of 2019 (COVID-19) is the clinical manifestation of the respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ***(Katneni et al., 2020)***. Patients with COVID-19 often present with dyspnea, hypoxemia, and hemodynamic instability with acute respiratory distress syndrome (ARDS), and in such clinical condition, venous thromboembolism (VTE) may be overlooked **(Iba *et al., 2020).***

Severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019 (COVID-19)-induced infection can be associated with a coagulopathy, findings consistent with infection-induced inflammatory changes as observed in patients with disseminated intravascular coagulopathy (DIC) **(Connors & Levy, 2020).**

Severe acute respiratory syndrome coronavirus 2/coronavirus disease 2019 frequently induces hypercoagulability with both microangiopathy and local thrombus formation, and a systemic coagulation defect that leads to large vessel thrombosis and major thromboembolic complications, including pulmonary embolism in critically ill hospitalized patients. d-dimers and fibrinogen levels should be monitored, and all hospitalized patients should undergo thromboembolism prophylaxis with an increase in therapeutic anticoagulation in certain clinical situations **(Iba *et al., 2020).***

Aim of the work

The aim of this study was to measure the plasma level of ADAMTS-13 in covid-19 patients and to correlate it's level with the prognosis of the disease and the clinical outcome of the patients.

Chapter One: Covid-19

Coronavirus is one of the major pathogens that primarily target the human respiratory system. Previously outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been characterized as agents that are a great public health threat. In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology. These patients were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China ***(Rothan & Byrareddy, 2020).***

According to the World Health Organization (WHO) February 2020, there had been >51,000 confirmed cases globally, leading to at least 1600 deaths. The emerging pathogen was rapidly characterized as a new member of the beta-coronavirus genus, closely related to several bat coronaviruses and to severe acute respiratory syndrome coronavirus (SARS-CoV) ***(Lu et al., 2020), (Wu et al., 2020).***

Coronavirus is discovered for the first time in the 1960s. Coronaviridae are a family of enveloped positive-sense single-stranded ribonucleic acid (RNA) viruses**.** The genome size of this viral group ranges between 27 and 34 kilobases, which is larger than most other RNA viruses ***(Sexton et al., 2016).*** The name Coronavirus originates from the Latin word corona, meaning “crown” or “halo”,

due to its characteristic appearance under two-dimensional transmission electron microscopy. Coronaviruses have club-shaped spike peplomers covering their surfaces **(Figure 1)** ***(Chorba, 2020).***

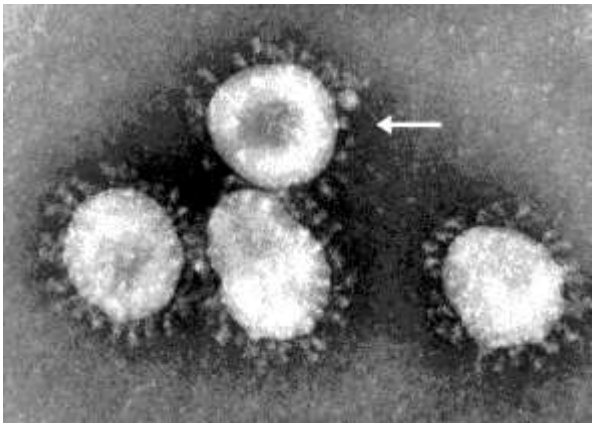

Figure (1): Coronaviruses electron microscope ***(Valencia, 2020)***

The 2019, CoV has a different coronavirus specific nucleic acid sequence from known human coronavirus species, which are similar to some of the beta coronaviruses identified in bats. The virus specific nucleic acid sequences were detected in lung fluid, blood and throat swab samples in 15 patients and the virus that was isolated showed a typical coronavirus appearance under electron microscopy. Further research will be conducted to better understand the new coronavirus to develop antiviral agents and vaccines ***(Lu et al., 2020).***

The current emergence of COVID-19 is the third CoV outbreak in humans over the past 2 decades ***(Dhama et al., 2020).*** Initial clinical and laboratory results focused on several known agents of respiratory illness, including human meta-pneumovirus, influenza