بسم الله الرحمن الرحيم

Shendi University

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Evaluation of Coagulation Parameters Among Vaccinated Covid19 Individual In Atbara Twon

A dissertation submitted in partial fulfillment for the requirement of M.Sc. degree in medical laboratory
Science –hematology

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2021

الآيه

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قال تعالي:
{أَمَّنْ هُوَ قَانِتٌ آنَاءَ اللَّيْلِ سَاجِدًا وَقَائِمًا يَحْذَرُ الآخِرَةَ وَيَرْجُو رَحْمَةَ رَبِّهِ
قُلْ هَلْ يَسْتَوِي الَّذِينَ يَعْلَمُونَ وَالَّذِينَ لا يَعْلَمُونَ إِنَّمَا يَتَذَكَّرُ أُولُواْ
الأَلْبَابِ}
صدق الله العظيم [سورة الزمر:9].

Dedication

To who have to taught me the life who trained me how me l can change to best

Dear father

To the depth of be longings and rhythm of sympathy

Soul mother

To crown of pleasure and secret of existence

To my husband

To partners of educational years
Friend and dear colleagues

Acknowledgment

First we would like to thanks our merciful Allah for giving us the power and health to do this work

We are really indebted with appreciation and gratefulness to our supervisor
Dr.EL-Fatih Mohammed Abdallah as sacrificed much of his time for suggestion and supervisor of this work

Special thanks to the all staff of hematology department and also to everyone let a hand to make this work possible

Abstract

Background: Covid19 vaccine is vaccine which is received to all individual to reduce the risk of symptoms of corona virus disease.

This study done at Atbara to evaluate the change in coagulation screening tests among individuals that received covid 19 vaccine

Aims: this study was aimed to evaluate coagulation profile (PT, APTT, INR) among people vaccinated with covid 19 vaccine.

Methodology: 100 venous sodium citrate blood sample were collected; thirty person is not vaccinated as control and seventy person was vaccinated against covid 19. This was cross sectional study conducted in Atbara city during the period from October to December 2021. 70 sample must be collected from vaccinated person and another 30-sample collected from un vaccinated person. All assay tests were determined by method- using semi-automated analyzer. Obtained results were analyzed using SPSS

Result: According to the result of this research show insignificant variation in PT PTT and INR between vaccinated and not vaccinated individual.

Conclusion: PT, INR were high with age, diabetes, hypertension, and warfarin in take patient with healthy individual in control group.

مستخلص البحث

الخلفية: لقاح كوفيد 19 هو لقاح يتم تلقيه لجميع الأفراد لتقليل خطر ظهور أعراض مرض فيروس كورونا .أجريت هذه الدراسة في عطبرة لتقييم التغيير في اختبارات فحص التخثر بين الأفراد الذين تلقوا لقاح كوفيد 19

الأهداف: هدفت هذه الدراسة إلى تقييم ملف التخثر (PT ، APTT، INR) بين الأشخاص الذين تم تطعيمهم بلقاح كوفيد 19 .

المنهجية: تم جمع 100 عينة دم وريدية من سترات الصوديوم؛ ثلاثون شخصًا غير مُلقحين كمجموعة تحكم وسبعون شخصًا تم تطعيمهم ضد كوفيد 19. أجريت هذه دراسة مقطعية في مدينة عطبرة خلال الفترة من أكتوبر إلى ديسمبر 2021. يجب جمع 70 عينة من شخص مُلقح و30 عينة أخرى من شخص غير مُلقح .تم تحديد جميع اختبارات التحليل بطريقة - باستخدام محلل شبه آلي .تم تحليل النتائج التي تم الحصول عليها باستخدام برنامج SPSS

النتيجة: وفقًا لنتيجة هذا البحث، تبين وجود اختلاف طفيف في PT PTT و INR بين الأفراد المطعمين وغير المطعمين.

الاستنتاج: كان PT و INR مرتفعين مع تقدم العمر ومرض السكري وارتفاع ضغط الدم والوارفارين في المريض الذي تناول الدواء مع فرد سليم في المجموعة الضابطة.

List of Abbreviations

Abbreviation	Full statement
Az	Astrazinca
INR	International normalized ratio
LNPS	Lipid nano particles
MHC	Major histocompatibility complex
ppp	Platelet poor plasma
PT	Prothrombin time
PTT	Activated partial thromboplastin time
SPSS	Statistical package for the Social Sciences
Th	T- helper
VITT	Vaccine induced thrombtic thrombocytopenia

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1.1 Introduction

Initially, COVID-19 vaccinations were issued without preference until it emerged that this risk was associated with the Oxford – AstraZeneca (AZ) or the Johnson & Johnson (J&J) vaccine. Subsequently, vaccinations were delayed and scaled back [(1).]

At first, there was great uncertainty and debate because similar conditions can occur naturally, and the initial rates of incidence were not greater than those expected to occur in the general population. Added to this was the fact blood clotting is also a complication of an infection with coronavirus itself [(1).]

As the link between clotting and the AZ and J&J vaccine was better affirmed, it became apparent that younger people were more at risk —possibly because of a more robust immune response to the vaccine. This article gives an overview of the risks of blood-clotting linked to certain vaccines and the response from officials, the research being done, and the symptoms to look out for this change[(2).]

Thrombosis is the formation of blood clot inside blood vessel, obstructing the blood flow through the circulatory system, when blood vessel is injured the body uses platelet and fibrin to form blood clot, when blood vessel is not injured blood clot may form in the body under certain condition clot or piece of clot begin to travel around the body is known as embolus.[(3)]

Venous thrombosis it more common when there is sluggish flow or stasis and endothelial changes, such thrombus is usually composed of abundant fibrin and many red cells. [(4)]

Arterial thrombosis Occure around the orifiaces of branches an bifurcation, it areas where turbulence an sheer stresses are greatest ,that endothelial injury and other tomato's change are most marked and platelet aggregation are

readily formed ,arterial thrombus thus formed has pale appearance due to predominance of platelet. [5]

Effects of thrombosis Thrombosis may produce local and distance effect .the local effect depend on the site and the degree of vascular occlusion and the remote effects are due to embolic phenomena or to the release of vaso active substances from the evolving thrombus into the passing stream of blood. Detachment and mobilization of various thrombi may produce obstruction within the pulmonary arterial system. [5]

The PT assay has two purposes: to screen for inherited or acquired deficiencies in the extrinsic and common pathways of coagulation and to monitor oral anticoagulant therapy.[6]

The APTT assay is useful for three reasons – as a screening test for inherited or acquired deficiencies of the intrinsic pathway, to detect inhibitors, and to monitor heparin therapy.[7]

D-dimer is fibrin degradation product (or FDP), a small protein fragment present in the blood after blood clot is degraded by fibrinolysis. [8]

The etiology of thrombosis is complex subject and in most cases is multi factorial .there is close relationship between thrombosis and development of atherosclerotic vascular disease (development from blood component by hemodynamic factor and platelet leucocytes interaction with vessel wall which may lead to endothelial injury and smooth muscle migration, by formation of persistent mural thrombi. [7]

1.2. Rational

Corona virus is world wide disease that affect many people in different age more dangerous in old age and people suffering from chronic diseases like diabetes and hypertensive and cardiac disease mmany types of vaccine has been developed to protect the people from the rapid transmisson of this virus, risks of blood-clotting linked to certain vaccines, this research conducted the evaluate coagulation screening test among the individuals that received the vaccine.

1.3 Objective

1.3.1 General Objective

To evaluate coagulation (PT, APTT, INR)among people vaccinated with covid 19 vaccine .

1.3. Specific Objectives:

I – To estimate (PT, APTT, INR) in vaccinated individual.

2- To correlate the result of test with control.

3- To correlate the result of test with possible risk factors (age, gender, etc.).

Chapter Two

Literature Review

2. Literature Review

2.1 Normal hemostatic mechanism

Coagulation, also known as clotting, is the process by which blood changes from a liquid to a gel, forming a blood clot. It potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion and aggregation of platelets, as well as deposition and maturation of fibrin(3).

Coagulation begins almost instantly after an injury to the endothelium lining a blood vessel. Exposure of blood to the subendothelial space initiates two processes: changes in platelets, and the exposure of subendothelial tissue factor to plasma factor VII, which ultimately leads to cross-linked fibrin formation. Platelets immediately form a plug at the site of injury; this is called primary hemostasis. Secondary hemostasis occurs simultaneously: additional coagulation (clotting) factors beyond factor VII (listed below) respond in a cascade to form fibrin strands, which strengthen the platelet plug(3)

Disorders of coagulation are disease states which can result in problems with hemorrhage, bruising, or thrombosis.[4]

Coagulation is highly conserved throughout biology. In all mammals, coagulation involves both a cellular (platelet) and a protein (coagulation factor) component.[5] The system in humans has been the most extensively researched and is the best understood.[6]

2.2. Platelet activation

When the endothelium is damaged, the normally isolated underlying collagen is exposed to circulating platelets, which bind directly to collagen with collagen-specific glycoprotein Ia/IIa surface receptors. This adhesion is strengthened further by von Willebrand factor (vWF), which is released from the endothelium and from platelets; vWF forms additional links between the

platelets' glycoprotein Ib/IX/V and A1 domain. This localizationof platelets to the extracellular matrix promotes collagen interaction with platelet glycoprotein VI. Binding of collagen to glycoprotein VI triggers a signaling cascade that results in activation of platelet integrins. Activated integrins mediate tight binding of platelets to the extracellular matrix. This process adheres platelets to the site of injury.[7]

Activated platelets release the contents of stored granules into the blood plasma. The granules include ADP, serotonin, platelet-activating factor (PAF), vWF, platelet factor 4, and thromboxane A_2 (TXA_2), which, in turn, activate additional platelets. The granules' contents activate a G_q-linked protein receptor cascade, resulting in increased calcium concentration in the platelets' cytosol. The calcium activates protein kinase C, which, in turn, 0activates phospholipase A_2 (PLA_2). PLA_2 then modifies the integrin membrane glycoprotein IIb/IIIa, increasing its affinity to bind fibrinogen. The activated platelets change shape from spherical to stellate, and the fibrinogen cross-links with glycoprotein IIb/IIIa aid in aggregation of adjacent platelets (completing primary hemostasis).[8]

2. 3. Coagulation cascade

The coagulation cascade of secondary hemostasis has two initial pathways which lead to fibrin formation. These are the contact activation pathway (also known as the intrinsic pathway), and the tissue factor pathway (also known as the extrinsic pathway), which both lead to the same fundamental reactions that produce fibrin. It was previously thought that the two pathways of coagulation cascade were of equal importance, but it is now known that the primary pathway for the initiation of blood coagulation is the tissue factor (extrinsic) pathway. The pathways are a series of reactions, in which a zymogen (inactive enzyme precursor) of a serine protease and its glycoprotein co-factor are

activated to become active components that then catalyze the next reaction in the cascade, ultimately resulting in cross-linked fibrin. Coagulation factors are generally indicated by Roman numerals, with a lowercase a appended to indicate an active form.[9]

The coagulation factors are generally serine proteases (enzymes), which act by cleaving downstream proteins. The exceptions are tissue factor, FV, FVIII, FXIII.[10] Tissue factor, FV and FVIII are glycoproteins, and Factor XIII is a transglutaminase.[9] The coagulation factors circulate as inactive zymogens. The coagulation cascade is therefore classically divided into three pathways. The tissue factor and contact activation pathways both activate the "final common pathway" of factor X, thrombin and fibrin.(11)

2.4. Tissue factor pathway (extrinsic)

The main role of the tissue factor pathway is to generate a "thrombin burst", a process by which thrombin, the most important constituent of the coagulation cascade in terms of its feedback activation roles is released very rapidly. FVIIa circulates in a higher amount than any other activated coagulation factor. The process includes the following steps:[9]

1. Following damage to the blood vessel, FVII leaves the circulation and comes into contact with tissue factor (TF) expressed on tissue-factor-bearing cells (stromal fibroblasts and leukocytes), forming an activated complex (TF-FVIIa).
2. TF-FVIIa activates FIX and FX.
3. FVII is itself activated by thrombin, FXIa, FXII, and FXa.
4. The activation of FX (to form FXa) by TF-FVIIa is almost immediately inhibited by tissue factor pathway inhibitor (TFPI).
5. FXa and its co-factor FVa form the prothrombinase complex, which activates prothrombin to thrombin.

6. Thrombin then activates other components of the coagulation cascade, including FV and FVIII (which forms a complex with FIX), and activates and releases FVIII from being bound to vWF.
7. FVIIIa is the co-factor of FIXa, and together they form the "tenase" complex, which activates FX; and so the cycle continues. ("Tenase" is a contraction of "ten" and the suffix "-ase" used for enzymes.)

2.5. Contact activation pathway (intrinsic)

The contact activation pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation can be illustrated by the fact that individuals with severe deficiencies of FXII, HMWK, and prekallikrein do not have a bleeding disorder. Instead, contact activation system seems to be more involved in inflammation,[9] and innate immunity.[12] Despite this, interference with the pathway may confer protection against thrombosis without a significant bleeding risk.[12]

2.6. Final common pathway

The division of coagulation in two pathways is arbitrary, originating from laboratory tests in which clotting times were measured either after the clotting was initiated by glass, the intrinsic pathway; or clotting was initiated by thromboplastin (a mix of tissue factor and phospholipids), the extrinsic pathway (9).

Further, the final common pathway scheme implies that prothrombin is converted to thrombin only when acted upon by the intrinsic or extrinsic

pathways, which is an oversimplification. In fact, thrombin is generated by activated platelets at the initiation of the platelet plug, which in turn promotes more platelet activation [(9).]

Thrombin functions not only to convert fibrinogen to fibrin, it also activates Factors VIII and V and their inhibitor protein C (in the presence of thrombomodulin); and it activates Factor XIII, which forms covalent bonds that crosslink the fibrin polymers that form from activated monomers.[9]

The coagulation cascade is maintained in a prothrombotic state by the continued activation of FVIII and FIX to form the tenase complex until it is down-regulated by the anticoagulant pathways.[9] Cell-based scheme of coagulation A newer model of coagulation mechanism explains the intricate combination of cellular and biochemical events that occur during the coagulation process in vivo. Along with the procoagulant and anticoagulant plasma proteins, normal physiologic coagulation requires the presence of two cell types for formation of coagulation complexes: cells that express tissue factor (usually extravascular) and platelets [(9).]

The coagulation process occurs in two phases. First is the initiation phase, which occurs in tissue-factor-expressing cells. This is followed by the propagation phase, which occurs on activated platelets. The initiation phase, mediated by the tissue factor exposure, proceeds via the classic extrinsic pathway and contributes to about 5% of thrombin production. The amplified production of thrombin occurs via the classic intrinsic pathway in the propagation phase; about 95% of thrombin generated will be during this second phase.[13]

2.7. Cofactors

Various substances are required for the proper functioning of the coagulation cascade:

Calcium and phospholipid

Calcium and phospholipid (a platelet membrane constituent) are required for the tenase and prothrombinase complexes to function. Calcium mediates the binding of the complexes via the terminal gamma-carboxy residues on FXa and FIXa to the phospholipid surfaces expressed by platelets, as well as procoagulant microparticles or microvesicles shed from them. Calcium is also required at other points in the coagulation cascade. .[13]

2.8.Vitamin K

Vit7min K is an essential factor to a hepatic gamma-glutamyl carboxylase that adds a carboxyl group to glutamic acid residues on factors II, VII, IX and X, as well as Protein S, Protein C and Protein Z. In adding the gamma-carboxyl group to glutamate residues on the immature clotting factors, Vitamin K is itself oxidized. Another enzyme, Vitamin K epoxide reductase (VKORC), reduces vitamin K back to its active form. Vitamin K epoxide reductase is pharmacologically important as a target of anticoagulant drugs warfarin and related coumarins such as acenocoumarol, phenprocoumon, and dicumarol. These drugs create a deficiency of reduced vitamin K by blocking VKORC, thereby inhibiting maturation of clotting factors. Vitamin K deficiency from other causes (e.g., in malabsorption) or impaired vitamin K metabolism in disease (e.g., in liver failure) lead to the formation of PIVKAs (proteins formed in vitamin K absence), which are partially or totally non-gamma carboxylated, affecting the coagulation factors' ability to bind to phospholipid. .[13]

2.9. Platelet disorders

Platelet disorders are either congenital or acquired. Examples of congenital platelet disorders are Glanzmann's thrombasthenia, Bernard–Soulier syndrome (abnormal glycoprotein Ib-IX-V complex), gray platelet syndrome

(deficient alpha granules), and delta storage pool deficiency (deficient dense granules). Most are rare. They predispose to hemorrhage. Von Willebrand disease is due to deficiency or abnormal function of von Willebrand factor, and leads to a similar bleeding pattern; its milder forms are relatively common. [18]

Decreased platelet numbers (thrombocytopenia) is due to insufficient production (e.g., myelodysplastic syndrome or other bone marrow disorders), destruction by the immune system (immune thrombocytopenic purpura/ITP), or consumption (e.g., thrombotic thrombocytopenic purpura/TTP, hemolytic-uremic syndrome/HUS, paroxysmal nocturnal hemoglobinuria/PNH, disseminated intravascular coagulation/DIC, heparin-induced thrombocytopenia/HIT).[18] Most consumptive conditions lead to platelet activation, and some are associated with thrombosis. [18]

2.10. Coagulation factor disorders

The best-known coagulation factor disorders are the hemophilias. The three main forms are hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency or "Christmas disease") and hemophilia C (factor XI deficiency, mild bleeding tendency).[19]

Von Willebrand disease (which behaves more like a platelet disorder except in severe cases), is the most common hereditary bleeding disorder and is characterized as being inherited autosomal recessive or dominant. In this disease, there is a defect in von Willebrand factor (vWF), which mediates the binding of glycoprotein Ib (GPIb) to collagen. This binding helps mediate the activation of platelets and formation of primary hemostasis.[medical citation needed]

In acute or chronic liver failure, there is insufficient production of coagulation factors, possibly increasing risk of bleeding during surgery.[19]

Thrombosis is the pathological development of blood clots. These clots may break free and become mobile, forming an embolus or grow to such a size that occludes the vessel in which it developed. An embolism is said to occur when the thrombus (blood clot) becomes a mobile embolus and migrates to another part of the body, interfering with blood circulation and hence impairing organ function downstream of the occlusion. This causes ischemia and often leads to ischemic necrosis of tissue. Most cases of venous thrombosis are due to acquired states (older age, surgery, cancer, immobility) or inherited thrombophilias (e.g., antiphospholipid syndrome, factor V Leiden, and various other genetic deficiencies or variants) .[19]

2.11. Assessment

Numerous tests are used to assess the function of the coagulation system:[14]

- Common: aPTT, PT (also used to determine INR), fibrinogen testing (often by the Clauss method), platelet count, platelet function testing (often by PFA-100), thrombodynamics test.
- Other: TCT, bleeding time, mixing test (whether an abnormality corrects if the patient's plasma is mixed with normal plasma), coagulation factor assays, antiphospholipid antibodies, D-dimer, genetic tests (e.g. factor V Leiden, prothrombin mutation G20210A), dilute Russell's viper venom time (dRVVT), miscellaneous platelet function tests, thromboelastography (TEG or Sonoclot), euglobulin lysis time (ELT). [16]

The contact activation (intrinsic) pathway is initiated by activation of the "contact factors" of plasma, and can be measured by the activated partial thromboplastin time (aPTT) test.

The tissue factor (extrinsic) pathway is initiated by release of tissue factor (a specific cellular lipoprotein), and can be measured by the prothrombin time

(PT) test. PT results are often reported as ratio (INR value) to monitor dosing of oral anticoagulants such as warfarin [16].

The quantitative and qualitative screening of fibrinogen is measured by the thrombin clotting time (TCT). Measurement of the exact amount of fibrinogen present in the blood is generally done using the Clauss method for fibrinogen testing. Many analysers are capable of measuring a "derived fibrinogen" level from the graph of the Prothrombin time clot. [16]

If a coagulation factor is part of the contact activation or tissue factor pathway, a deficiency of that factor will affect only one of the tests: Thus hemophilia A, a deficiency of factor VIII, which is part of the contact activation pathway, results in an abnormally prolonged aPTT test but a normal PT test. The exceptions are prothrombin, fibrinogen, and some variants of FX that can be detected only by either aPTT or PT. If an abnormal PT or aPTT is present, additional testing will occur to determine which (if any) factor is present as aberrant concentrations. [16]

Deficiencies of fibrinogen (quantitative or qualitative) will affect all screening tests. [16]

2.12. corona virus

Corona viruses are large, enveloped, single-stranded RNA viruses found in humans and other mammals, such as dogs, cats, chicken, cattle, pigs, and birds. Coronaviruses cause respiratory, gastrointestinal, and neurological disease.[3].

The most common coronaviruses in clinical practice are229E, OC43,NL63, and HKU1,which typically cause common cold symptoms in immunocompetent individuals. SARS-CoV-2 is the third coronavirus that has caused severe disease in humans to spread globally in the past 2 decades. [15]

The first coronavirus that caused severe disease was severe acute respiratory

Syndrome (SARS), which was thought to originate in Foshan, China, and resulted in the2002-2003SARS-CoVpandemic. [18]

The second was the coronavirus-caused Middle East respiratory syndrome (MERS), which originated from the Arabian peninsula in 2012. [19]

SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona [18] Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be a natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARS CoV-2 via an intermediate host, such as the pangolin. [21] [22]

SARS-CoV-2 is spread primarily via respiratory droplets during close face-to-face contact. Infection can be spread by asymptomatic, pre symptomatic, and symptomatic carriers.

The average time from exposure to symptom onset is 5 days, and 97.5%of people who develop symptoms do so within 11.5 days.

The most common symptoms are fever, dry cough, and shortness of breath. Radiographic and laboratory abnormalities, such as lymphopenia and elevated lactate dehydrogenase, are common, but nonspecific. Diagnosis is made by detection of SARS-CoV-2 via reverse transcription polymerase chain reaction testing, although false-negative test results may occur in up to 20%to 67%of patients; however, this is dependent on the quality and timing of testing. [23]

Manifestations of COVID-19 include asymptomatic carriers and fulminant disease characterized by sepsis and acute respiratory failure. Approximately 5%of patients with COVID-19, and 20%of those hospitalized, experience severe symptoms necessitating intensive care. More than 75%of patients hospitalized with COVID-19 require supplemental oxygen. Treatment for

individuals with COVID-19 includes best practices for supportive management of acute hypoxic respiratory failure. [23]

Emerging data indicate that dexamethasone therapy reduces 28-day mortality in patients requiring supplemental oxygen compared with usual care (21.6%vs 24.6%; age-adjusted rate ratio, 0.83 [95%CI,0.74-0.92]) and that remdesivir improves time to recovery (hospital discharge or no supplemental oxygen requirement) from 15 to 11 days. In a randomized trial of 103 patients with COVID-19, convalescent plasma did not shorten time to recovery. Ongoing trials are testing antiviral therapies, immune modulators, and anticoagulants The case-fatality rate for COVID-19 varies markedly by age, ranging from 0.3 deaths per 1000 cases among patients aged 5 to 17 years to 304.9 deaths per 1000 cases among patients aged 85 years or older in the US. [24].

Among patients hospitalized in the intensive care unit, the case fatality is up to 40%. At least 120 SARS-CoV-2 vaccines are under development. Until an effective vaccine is available, the primary methods to reduce spread are facemasks, social distancing, and contact tracing. Monoclonal antibodies and hyper immune globulin may provide additional preventive strategies. [25]

2.12.1. Pathophysiology

The SARS-CoV-2 infection enters the host cells through the S spike protein by binding to ACE2 for internalization and aided by TMPRSS2 protease. The high infectivity of the virus is related to mutations in the receptor binding domain and acquisition of a furan cleavage site in the S spike protein. The virus interaction with ACE2 may downregulate the anti-inflammatory function and heighten angiotensin II effects in predisposed patients. [26] With the challenge we face with COVID-19, some have been advocating for the use (or cessation) of Angiotensin II receptor type 1 (AT1 receptor) blockers and ACE inhibitors during the treatment of COVID-19 in patients with

hypertension. Currently the recommendation of the Council on Hypertension of the European Society of Cardiology is that patients should continue their antihypertensive treatment with no changes because we do not have evidence supporting its cessation. [26] However, further research is needed to back these recommendations with more evidence. [28]

The invasion of the virus to the lung cells, myocytes and endothelial cells of the vascular system results in inflammatory changes including oedema, degeneration and necrotic changes. These changes are mainly related to proinflammatory cytokines including interleukin (IL)-6, IL-10 and tumor necrosis factor α, granulocyte colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and increased expression of programmed cell death 1, T-cell immunoglobulin and mucin domain 3 (Tim-3) [27]These changes contribute to lung injury pathogenesis, hypoxia-related myocyte injury, body immune response, increased damage of myocardial cells, and intestinal and cardiopulmonary changes.

Infection with SARS-CoV-2 has been also shown to cause hypoxaemia. These changes lead to accumulation of oxygen free radicals, changes in intracellular pH, accumulation of lactic acid, electrolyte changes and further cellular damage. [27]

2.12.2. The Host Defense against Covid-19

Early in infection, SARS-CoV-2targets cells, such as nasal and bronchial epithelial cells and pneumocystis, through the viral structural spike(S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. [26]The type 2 transmembrane serine protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which mediates corona virus entry into host cells.

ACE2andTMPRSS2areexpressedinhost Target cells, particularly alveolar epithelial typell cells. Similar to other [29] [30]

Respiratory viral diseases, such as influenza, profound lymphopenia may occur in individual's withCOVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition, the viral inflammatory response, consisting of both the innate and the adaptive immune response (Comprising humoral and cell-Mediated immunity), impairs lymphopoiesis and increases lymphocyte apoptosis although up regulation of ACE2 receptors from ACE inhibitor and angiotensin Receptor blocker medications [29]

Has been hypothesized to increase susceptibilitytoSARS-CoV-2infection, Large observational cohorts have not found an association between these medications and risk of infection or hospital mortality due to COVID-19For exampl [31]e, in a study 4480 patients withCOVID-19 from Denmark, previous treatment with ACE inhibitor so angiotensin receptor blockers was not associated with mortality. [31]

In later stages of infection, when viral replication accelerates, epithelial-endothelial barrier integrity is compromised. In addition to epithelial cells, SARS-CoV-2infects pulmonary capillary endothelial cells, accentuating the inflammatory response and triggering an influx of monocytes and neutrophils. Autopsy studies have shown diffuse thickening of the alveolar wall with mononuclear cells and macrophages infiltrating air spaces in addition to endothelialitis. [32]

Interstitial mononuclear inflammatory infiltrates and edema develop and appear as ground-glass opacities on computed tomographic imaging. Pulmonary edema filling the alveolar spaces with hyaline membrane formation follows, compatible with early-phase acute respiratory distress syndrome (ARDS). Brady [33]kinin-dependent lung angioedema may

contribute to disease. [34] Collectively, endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission, and impaired oxygen diffusion capacity are characteristic features of COVID-19.

In severeCOVID-19, fulminant activation of coagulation and consumption of clotting factors occur. [35] [36] report from Wuhan, China, indicated that 71%of 183 individuals who died of COVID-19 met criteria for diffuse intravascular coagulation. [36]

Inflamed lung tissues and pulmonary endothelial cells may result in micro thrombi formation and contribute to the high incidence of thrombotic complications, such as deep venous thrombosis, pulmonary embolism, and thrombotic arterial complications (eg, limb ischemia, ischemic stroke, myocardial infarction)

In critically ill patients. [36] The development to viral sepsis, defined as life threatening organ dysfunction caused by a dysregulated host response to infection, may further contribute to multiorgan failure.

Clinical Presentation of covid-19

Fever or chills, Cough, Shortness of breath or difficulty breathing

Fatigue, Muscle or body aches, Headache, New loss of taste or smell

Sore throat, Congestion or runny nose, Nausea or vomiting, Diarrhea

2.12.3. Modes of transmission of the COVID-19 virus

Respiratory infections can be transmitted through droplets of different sizes: when the droplet particles are >5-10 μm in diameter they are referred to as respiratory droplets, and when then are <5μm in diameter, they are referred to as droplet nuclei. [37] According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes [38]in an analysis of 75,465 COVID-19 cases in China, airborne transmission was not reported. [39]

Droplet transmission occurs when a person is in in close contact (within 1 m) with someone who has respiratory symptoms (e.g., coughing or sneezing) and is therefore at risk of having his/her mucosae (mouth and nose) or conjunctiva (eyes) exposed to potentially infective respiratory droplets. Transmission may also occur through fomites in the immediate environment around the infected person. [40] Therefore, transmission of the COVID-19 virus can occur by direct contact with infected people and indirect contact with surfaces in the immediate environment or with objects used on the infected person (e.g., stethoscope or thermometer). [40]

Airborne transmission is different from droplet transmission as it refers to the presence of microbes within droplet nuclei, which are generally considered to be particles <5μm in diameter, can remain in the air for long periods of time and be transmitted to others over distances greater than 1 m.

In the context of COVID-19, airborne transmission may be possible in specific circumstances and settings in which procedures or support treatments that generate aerosols are performed; i.e., endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation. [40]

There is some evidence that COVID-19 infection may lead to intestinal infection and be present in faeces. However, to date only one study has cultured the COVID-19 virus from a single stool specimen. [41] There have been no reports of faecal−oral transmission of the COVID-19 virus to date.

2.13. Most Common Anti-Covid-19 Vaccines

2.13.1. Pfizer-BioNTech (Comirnaty) BNT 162b2 and Moderna (1273)

This method utilizes lipid nanoparticles (LNPs) with a formulated mRNA vaccine. This work was fast-tracked at an unprecedented pace, even though mRNA-based vaccines have never been licensed before. [42] RNA vaccines belong to a cutting-edge approach that uses genetically engineered RNA to generate a protein that safely prompts an immune response. [43]

mRNA-based vaccines have the greatest potential for rapid development because of their synthetic nature that circumvents the need for cell culture or fermentation of viruses. Due to their high potency, rapid development and low cost for manufacturing, mRNA vaccines have emerged as a promising alternative vaccination development strategy for various infectious diseases and cancers. [44]

2.13.1.1.Mechanism of Action

The SARS-CoV-2 contains 25–28 proteins but the researchers just isolated the mRNA from the spike protein which shows 3 copies of the same protein, then only one mRNA is produced. (Several strategies have been proposed to solve the common drawbacks of mRNA-based vaccines, which include the mRNA instability with respect to DNA. In fact the mRNA lasts up to two days in our body, it is easy to degrade and requires high cold chain. The storage temperature of Pfizer-BioNTech Covid-19 vaccine was −94° Fahrenheit corresponding to −70°Celsius. [44] Vaccine storage in this case is a problem for low and medium countries income (LMCI). Nevertheless, in these vaccines, no adjuvants or preservatives are used because the vaccine is stimulated by itself. Moreover, the mRNA is included in a lipid particle which preserves its integrity and allows it not to get confused with other RNA molecules. [45]

From the SARS- CoV-2 virus, the mRNA (able to translate and codify for the superficial spike proteins of the virus involved in the human pathogenicity) by working from the way backwards of s-proteins, is isolated and included in a lipid nanoparticle. [46]This nanoparticle is injected intramuscularly into the human body and once attached to the host cells, inserts its mRNA into the cytoplasm (not in the nucleus) in such a way as to reach the ribosomes and use them for synthesizing the viral spike proteins. This process is called translation. [47] Proteins then achieve the cellular membrane and evolve in two types: the MHC-2 (antigen presenting cells) and the MHC-1 related to another antigen which is present in all the nucleated cells of our body. The MHC-2 complex is only found in particular kind of cells: B-cells, macrophages and dendritic cells. These are activated by the s-protein and attract the cells of the immune system. In particular, the T-helper (Th) cells which have a particular type of membrane protein (TCR) that binds to the viral s-protein. Other proteins called CD4 produced by the Th cells interact with the complex MHC-2. The strongly activated Th cells begin to produce cytokines such as IL-2, IL-4 and IL5. [48] These interleukins cause the B-cells of our body to differentiate into plasma-cells that begin to produce a huge amount of antibodies against the viral spike proteins, able to neutralize or destroy the virus. Meanwhile, the interleukins also stimulate Th cells to proliferate the memory T cells. Another group of cells called T-cytotoxic cells (Tcx cells) interact with the MHC-1 protein on the cell membranes through their TCR and produce CD8 proteins. These proteins are very dangerous because may allow the Tcx cells to generate unsafe molecules which lead the cells to death if infected with the virus in the future but not the cells which are currently processing the vaccine. [48]Conversely, these Tcx cells are also able to produce substances that amplify the aforementioned immune response (48).

2.13.2. Astra-Zeneca Oxford

AstraZeneca produced a viral vector vaccine using a genetically engineered virus that cannot cause disease, but that encodes coronavirus proteins to safely generate an immune response. This vaccine was initially used in the UK and has been available in Italy and Poland since the 9th of February 2021[(44).]

2.13.2.1.Mechanism of Action

The AstraZeneca vaccine uses a modified chimpanzee DNA adenovirus, which has not been exposed to human populations and does not generate an immune response to the adenovirus itself, but only to the viral protein encoded in the host DNA. [47]The DNA vector encodes a protein similar to the viral s-peptide to generate an immune response against it. The DNA vector is used as a template in human cells to generate new chimpanzee adenovirus replicas and produce the viral protein that elicits an immune response. Briefly, the chimpzee adenovirus is injected into humans and it latches to the host cells. The DNA gets released into the cytoplasm and later migrate into the cell nucleus. It does not get incorporated into the cellular DNA, but uses the host enzymes to get converted into mRNA that migrates back into the cytoplasm and interacts with host cell ribosomes (free or bound to the endoplasmic reticulum), resulting into translated proteins. The proteins get expressed on the cell membranes forming MHC1 and MHC2 complexes. At this point, the mechanisms of RNA and DNA vaccines is similar and leads to the activation of T-, B-, and plasma cells and antibodies [49]

2.13.3. Janssen (Johnson & Johnson)

An investigational Covid-19 vaccine developed by Janssen Pharmaceuticals (Johnson & Johnson, USA) appears to be safe and effective at preventing moderate and severe Covid-19 in adults [49] ·The vaccine, called Ad.26.COV2.S or JNJ-78436725 needs a single injection and can be stored in

a refrigerator for months (it does not require extreme cold-storage environments because it is not mRNA-based). This vaccine acts through an adenovirus engineered in a laboratory[49]. On March 1st 2021, the US FDA issued an emergency use authorization (EUA) for this vaccine to be distributed in the United States in individuals 18 years and older for the prevention of Covid-19. Afterwards, on March 12th of the same year, the EMA and the AIFA authorized the vaccine in Italy based on its efficacy to prevent severe forms of the disease including hospitalizations and deaths, which reaches 77% after 14 days of the administration and 85% after 28 days. Currently available data showed a similar efficacy in individuals over 65 years. This vaccine was approved in Italy in April. It has been used for some time and was then withdrawn due to important side effects but subsequently it was put back again on the market. [49]

2.13.3.1. Mechanism of Action

This vaccine employs a harmless cold virus (adenovirus 26 CoV2) to deliver a gene that carries the blueprint for the spiky protein found on the surface of the coronavirus. The mechanism of action of the vaccine is similar to that of the AstraZeneca vaccine. An adenovirus vector manipulated in the laboratory carries genetic information for the spike-protein in the viral DNA that can generate a specific mRNA[49]. The DNA portions of this adenovirus that would allow it to replicate were deleted from the vector, and consequently, the vector cannot get replicated in human cells. The vaccine is injected into the individuals, and the vector latches onto human cells, where the DNA carrying the information for the SARS-CoV-2 spike protein is transferred into the nucleus without being incorporated into the host cell DNA[49]. The strand of the viral DNA that would normally tell the cell to make more adenovirus particles, gets translated into mRNA that gets transported out into the

cytoplasm, where the cell machinery instead of making adenovirus particles produces spike protein. At this point, the viral spike proteins at the surface of the cells induce production of T-cells (CD4 and CD8), cytotoxic cells, plasma cells, ILs, and B-cells that constitute the three primary immune responses (antibodies, Killer CD8 T-cells and helper CD4T-cells) to block the infection" T-cells are cru[50][51]cial for destroying infected human cells, and the antibodies are effective to protect uninfected cells when free viral particles are circulating out of cells (antibodies can easily latch onto spike proteins on the viral surface). [52]

2.14. Problems Related to the mRNA and DNA Vaccines

It is well known that RNA is highly degradable and may last only up two days in our body. As a result of this, it must be protected in a lipoprotein particle before being injected to the population. Besides, the mRNA vaccines (Pfizer and Moderna) show the inconvenience of storage temperature. Indeed in order to preserve their activity, it is necessary to keep these vaccines at very low temperatures (−70°C or −20°C). This is a huge drawback for poor countries with a low standard of living. [52]

As for DNA vaccines such as E-Vax, more specific and complex equipment is necessary even if DNA is a stable molecule. Among the technologies available for vaccine development, DNA vaccination is a promising alternative to conventional vaccines because of its ability to elicit both humoral and cellular immune responses. Compared to mRNA vaccines, there are relevant advantages regarding producibility, stability, and mainly the storage that does not require very low temperatures what constitutes a big issue for the transport and conservation in nations at low income. [52]

2.15. New Vaccines Still in Progress

Novavax (NVX), Reithera, Sinovac or Coronovax, Curevac, VXA-CoV2.

2.16. Possible Side effects After Getting a COVID-19 Vaccine

On the arm: Pain, Redness, Swelling

2.17. Throughout the rest of your body

Tiredness, Headache, Muscle pain, Chills, Fever, Nausea.

2.18. Association between coagulation disorder and COVID-19

The association between COVID-19 and blood clots was recognized early in the pandemic among hospitalized COVID-19 patients. These patients experienced blood clots both in deep veins and arteries, which sometimes led to strokes and heart attacks. Although these conditions have mostly been seen in patients with severe COVID-19 illness, people with moderate illness have also developed blood clots. Data from the beginning of the pandemic indicated that the incidence of blood clots in severe COVID-19 illness ranged from 20 to 40 percent. The incidence in people with mild or moderate COVID-19 illness was three to nine percent. [53]

2.19. People have a higher risk for developing blood clots if they have COVID-19

Patients who develop blood clots as a result of COVID-19 infection usually have severe COVID-19 illness (hospitalized in the ICU), respiratory failure, require high amounts of oxygen, or have other underlying illnesses.

Other underlying risks for blood clots include patients with a previous medical history of blood clots or a hereditary blood clotting disorder. Those who have hypertension, diabetes, are obese, or have cancer are also at higher risk. [53]

2.20 Previous study

2.20.1. Association between AstraZeneca (AZ) vaccine and blood clotting

Researchers raised concerns after reports of an extremely rare but serious side effect of vaccination against the coronavirus —that of blood clotting. Both the

AstraZeneca vaccine and the Johnson & Johnson vaccine use adenovirus thought to trigger the rare both sometimes fatal clotting reaction. [54]

The life-threatening condition is known by researchers as vaccine-induced immune thrombotic thrombocytopenia (VITT), affecting just over 10 people in every one million dosed with the vaccine. Incidences of VITT were found to be less common vectors in recipients of the J&J vaccine. [54]

The risk of VITT after AZ vaccination was discovered to be higher after the first dose has been administered. It occurred more frequently in younger people, usually between 4 days and 4 weeks after vaccination. A UK study found that of 220 people diagnosed with VITT between March and June 2021 49 subsequently died [55]

Since these initial cases were reported the Joint Committee on Vaccination and Immunisation (JCVI) advised that those under 40 years of age should receive an alternative vaccine to the AZ vaccine in the UK. After these recommendations were made the incidence of VITT declined dramatically. [56]

2.20.2 Association between COVID-19 Vaccine Janssen and coagulation defects

At its meeting of 20 April 2021, EMA's safety committee (PRAC) concluded that a warning about unusual blood clots with low blood platelets should be added to the product information for COVID-19 Vaccine Janssen. PRAC also concluded that these events should be listed as very rare side effects of the vaccine. [57]

In reaching its conclusion, the Committee took into consideration all currently available evidence including eight reports from the United States of serious cases of unusual blood clots associated with low levels of blood platelets, one of which had a fatal outcome. As of 13 April 2021, over 7 million people had received Janssen's vaccine in the United States. [57]

All cases occurred in people under 60 years of age within three weeks after vaccination, the majority in women. Based on the currently available evidence, specific risk factors have not been confirmed. [57]

PRAC noted that the blood clots occurred mostly at unusual sites such as in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) and in arteries, together with low levels of blood platelets and sometimes bleeding. The cases reviewed were very similar to the cases that occurred with the COVID-19 vaccine developed by AstraZeneca, Vaxzevria. [57]

2.20.3 vaccine-induced thrombotic thrombocytopenia (VITT)

It was discovered in March 2021 in connection to the AstraZeneca COVID-19 vaccine and then later with the Johnson & Johnson COVID-19 vaccine. In rare cases, antibodies that the body produces as a side effect of the vaccine lead to uncontrolled activation of platelets. This causes both low platelet counts and blood clots to form in unusual areas. VITT is not associated with the Moderna or Pfizer-BioNTech mRNA vaccines. [58]

Symptoms of VITT include:

Severe or persistent headaches, Chest pain, Trouble breathing, Leg swelling/pain, Severe abdominal pain, Confusion, Vision changes.

Chapter Three

Materials and Methods

3. Materials and Methods

3.1 Study design

This is case control and hospital based study .

3.2.Study Area and duration:

The study was conducted inRiver nile state duration between july 2021 to Decemper2021.

3.3.Study Population

people vaccinated with covid 19 vaccine and people not vaccinated with covid 19 vaccine .

3.4.Inclusion Criteria:

Individual only vaccinated with coviad 19 vaccine were included in the study.

3.5.Exclusion Criteria:

Individual whom have a history of Chronic liver disease and diabetes.

3.6. Studyof Sample :

Individual were inoculated with covid 19 vaccine were selected and data collected using self administrated percoded questionnaire which was specifically designed to obtain information that helped in study

3.7.Sample size:

This study included 70 cases and 30 control individuals

3.8.Data Collection :

Data were collectedn using questionnaires, this questionnaire was specifically designed to collect information about age, sex, choronic disease, warfarin intake and type of vaccine.

3.9 Method

3.9.1.BIood Sample Collection and processing

Venous blood was collected using sterile disposable plastic syringe after cleaningth eveni puncture area with70%ethanol ,the blood was add to the anti coagulant at ratio of 4.5ml to.5 ml of citrate(3.2%(0.109M) buffered sodium citrate and gently mixed.

The sample was centrifugeat 1300rpm for 15 min to obtain platelet poor plasma(ppp).The ppp placed into plastic tubes,capped and frozenat-700Cusedfor PT,APTT.

3.9.2. Principle prothrombintime(PT)

The PT test measures the clotting time of recalcified plasma in the presence of an optimal concentration of tissue extract(thromboplastin)and indicates the overall efficiency of the extrinsic clotting system [58]

3.9.2.1. Assay procedure for PT

Cuvettes were placed in incubation area for prewarming at37c for 3minute at least. 100ml of prewarmed (37c) control or patient PPP was dispensed in cuvette in incubation area.

Then cuvettes transferred to test area and 200ul of well mixed calcified thromboplasin reagent were added to cuvette,the analyzer time rstarted automatically when reagent was added. When clot formed timer was stopped automatically asresult of OD changes,the analyzer is bichannel, get the mean of .the two tested cuvettes and expressitas PTon instrument display screen per seconds.Activated partial thromboplastin time(APTT) [58]

3.9.3.Principle of APTT:

The APTT was performed by automated testing in the batch or state mode.in the APTTan aliquot of undiluted,platelet poor plasma was incubated at 37co with aparticulat e factorXII activator (i.e., silica, celite, kaolin, ellagicacid,

etc. reagent containing phospholipids(partial thromboplastin) was added, followed by CaC12. the time required for clot formation after the addition of CaC12.it measure over all activity of inintrinsic pathway [60]

3.9.3.1.Assay procedure for PTT

Cuvettes were placed in incubation area for prewarming at37c for3minutes atleast. 100ml of prewarmed(37c)control or patient PPP was dispensed in cuvette in incubation area. After3minutes incubation 100ul of calcium chloride were added to each cuvette after they transferred to test area. When clot formed timer was stopped automatically asresult of OD changes,the analyzer isbichannel , get the mean of the two tested cuvettes and expressitas[60]

APTTon instrument display screen per seconds.

3.10 Ethical considerations

Participants were informed verbally in their simple language about the research, its benefits and method of sample collection, then their approval taken.

3.11 Data analysis

The statistical analysis of the results was performed by using the Statistical Package for Social Sciences(SPSS)using one independent T-test and correlation for testing significant and frequencies

Chapter Four

Results

Results

A total of only 100 blood sample were taken from vaccinated covid19 individual, the data show the mean of PT, PTT was (13.1) and (31.9) respectively and INR was (1.1). All the results were within the normal range and there was no statistically variation as shown in Table (4-1)

Table (4.1): Comparison between case and control in PT, PTT and INR:

Groups		**No**	**Mean**	**SD**	**P. value**
PT	Case	70	13.110	1.0679	0.668
	Control	30	13.177	1.1233	
PTT	Case	70	31.936	3.8650	0.113
	Control	3019	28.837	2.0737	
INR	Case	70	1.1603	0.11334	0.989
	Control	30	0.12646	0.12646	

Also this study show the mean values of PT,PTT and INR in male and female group Table (4-2)

Table (4.2): Comparison between gender in PT, PTT and INR:

Groups	Gender	No	Mean	SD	P. value
PT	Male	32	13.184	1.1156	0.596
	Female	38	13.047	1.0368	
PTT	Male	32	32.306	3.8190	0.466
	Female	38	31.624	3.9267	
INR	Male	32	1.1672	0.10663	0.644
	Female	38	1.1545	0.11981	

The mean values of PT, PTT and INR in different age group, show in Table(4-3).

Table (4.3): Comparison between age in PT, PTT and INR:

Groups	**Age**	**No**	**Mean**	**SD**	**P. value**
PT	20-30 years	22	12.914	0.7912	0.031
	31-45 years	33	12.995	0.8871	
	> 45 years	15	13.740	1.5296	
PTT	20-30 years	22	32.841	4.7321	0.420
	31-45 years	33	31.303	3.2310	
	> 45 years	15	32.000	3.7331	
INR	20-30 years	22	1.1450	0.09012	0.086
	31-45 years	33	1.1452	0.09355	
	> 45 years	15	1.2160	0.16400	

The mean values of PT,PTT and INR between different types of vaccine were show in Table(4-3).

Table (4.4): Comparison between types of vaccine in PT, PTT and INR:

Groups	Types of vaccine	No	Mean	SD	P. value
PT	Pfizer-Biontech	57	13.032	1.0202	0.200
	Janssen (Johnson & Johnson)	13	13.454	1.2421	
PTT	Pfizer-Biontech	57	31.714	3.8920	0.319
	Janssen (Johnson & Johnson)	13	32.908	3.7346	
INR	Pfizer-Biontech	57	1.1532	0.11388	0.274
	Janssen (Johnson & Johnson)	13	1.1915	0.10976	

The mean of PT, PTT and INR between different type of chronic diseases show in Table (4-5).

Table (4.5): Comparison between chronic disease in PT, PTT and INR:

Groups	**Chronic disease**	**No**	**Mean**	**SD**	**P. value**
PT	Diabetic	19	13.421	1.4332	0.025
	Hypertension	8	13.813	1.6084	
	Not have	43	12.842	0.5921	
PTT	Diabetic	19	31.095	2.6722	0.238
	Hypertension	8	31.725	3.9799	
	Not have	43	32.347	4.2825	
INR	Diabetic	19	1.1905	0.13155	0.043
	Hypertension	8	1.2263	0.18754	
	Not have	43	1.1603	0.07688	

The mean of PT, PTT, INR and significant value for person intake and not intake warfarin therapy show in Table (4-6).

Table (4.6): Comparison between warfarin in PT, PTT and INR:

Groups	Warfarin	No	Mean	SD	P. value
PT	Intake	5	14.860	1.9411	0.000
	Not intake	65	12.975	0.8581	
PTT	Intake	5	33.920	4.0394	0.236
	Not intake	65	31.783	3.8411	
INR	Intake	5	1.3440	0.16211	0.000
	Not intake	65	1.1462	0.09679	

Chapter Five

Discussion – Conclusion & Recommendations

5.1. Discussion

This is case control study to evaluate coagulation screening test among vaccinated against covid 19, the data show insignificant variation of the PT, PTT, and INR, which agree with the published data that done by Gold smith and his et al. [57]

The data of activated partial thromboplastin time also showed insignificant variation when compare with control (P. value >0.05) this study also agreement with the data that published by gold smith and his et al [57]

The result of laboratory investigation done show not significant statistical difference observed in INR compare with control group (P.value 0.9) in table (4-10), this result confirm byresult made by Lamjt and his et al[58]

The result of test conducted showed No difference apper between male and female in INR (P.value 0.6), this study agree with result made by Michael A[59].

The result of this study showed PT significant associated with age compare with control (p.value 0.03) this study is not agree with study made byFouchier RA .[60]

According to the result of laboratory investigation done showed not significant statistical difference association with gender in PT ,PTT,INR.when compare with control p.value (0.21 - 0.3 - 0.27)respectively. This result was agree with study made by Zhang D ,Wangw and et al in china.

The current study found that significant increase in mean of PT, INR in chorionic disease (diabetic and hypertension) compare with control group p.value 0.025 – P.value 0.04 respectively . and not significant with PTT P.value(0.2) , this study are not agree with studymade by Toshio team in Jaban

The result of this study was significant increase mean of PT ,INR association

with warfarin intake compare to control (P.value 0.00), PTT showed that there was little difference(p.value 0.236).

5.2. Conclusion

- There is no significant different in coagulation screening test (PT, PTT, INR) of person received covid 19 vaccine when compare with control group.
- PT, INR were high with age, diabetes, hypertension, and warfarin in take patient with healthy individual in control group.

5.3. Recommendation

- There is no change in evaluation of coagulation screening test (PT, PRR, INR) in person received covid19 vaccine.
- Must be evaluated another clotting test (D.dimer, fibrinogen level and factor assay).
- Further studies using large sample size should be conducted.
- Further studies should be conducted in patient using heparin therapy.

Chapter Five

References & Appendix

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