Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.05.051

Alteration of lipid profile, kidney functions, D-dimer and some anti- inflammatory parameters in samples of Iraqi patients with Covid-19

Noor Ghassan Elias[1], Raghda Shams Akram[2*], Yassamen Samer Abd Aon[3]
[1]Middle Technical University College of Health and Medical Techniquse, Baghdad, Iraq
[2]Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Baghdad, Iraq
[3]National Diabetes Center, Mustansiriyah University, Baghdad-Iraq
***Corresponding author:** Raghda Shams Akram, Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Baghdad, Iraq, Email: raghda.shams@uomustansiriyah.edu.iq

Submitted: 01 January 2023; Accepted: 04 February 2023; Published: 03 March 2023

ABSTRACT

Objective: The Aim of our research was to look into the association between various biochemical indicators and COVID-19 infection in Baghdad, Iraq.

Methods: From the 15th of March to the August 2022, a cohort of 45 people with positively COVID-19 and 45 healthy controls visited Al-Yarmouk Teaching Hospital in Baghdad, Iraq. All of the patients have been diagnosed with COVID-19 and are experiencing symptoms and indicators. Each of the patients and healthy controls had their whole blood samples taken to be analyzed for; Lipid profile (triglycerides, Total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein (HDL) values) Kidney function test (Urea and Creatinine), by using an enzymatic method , Anti-inflammation parameters (INF-, TGF, Interleukin—12, and Interleukin 18), The (Biosours) ELISA kit was used to assess the results., and D-dimer was quantified using mini vidas kits donated by Bio Meriux-France.

Results: The results showed that The majority of COVID-19 patients showed elevated lipid profiles and kidney function tests, as well as the anti-inflammatory parameters with increase the levels of D-dimer compared to healthy controls.

Conclusion: The present study concludes that Covid-19 cause alteration in lipid profile, kidney functions, D-dimer and some anti- inflammatory parameters.

Keywords: *Five Minute Preceptor, critical thinking, nursing profession students*

INTRODUCTION

The virus that causes COVID-19 is an enveloped, single-stranded, positive-sense RNA virus belonging to the Coronaviridae family. It belongs to the Nidovirales family of viruses, It can cause a variety of respiratory and gastrointestinal illnesses, ranging in severity from a simple cold to MERS and SAR (1).

Structures, energy sources, signaling mediators, and functions in infections, particularly viral infections, are all played by lipids (2) Lipids are involved in a number of macrophage regulatory and immune-modulation mechanisms.(3) It has also been discovered that lipid metabolism has a role in lung infections and inflammatory conditions. (4)

Prior to the current epidemic, coronaviruses were found to alter lipid metabolism and serum lipid profile items. Several investigations have found significant alterations in the lipid profile of COVID-19 infected patients (5).

Changes in innate and adaptive immunity are linked to chronic kidney disease (CKD) (6). In patients with CKD, both the risk of pneumonia and the incidence of pneumonia-related death are higher than in the general population (7). According to the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA), COVID-19 infection and related death are more common in CKD patients (8). According to recent studies, acute kidney damage (AKI) has also been connected to mortality in coronavirus infections, specifically COVID-19., (9). Formal research on the impact of admission renal function on COVID-19 mortality are, however, scarce.

The fibrinolytic system degrades the fibrin mesh after the clot has formed. The D-dimer, which is composed of two D fragments of fibrin, is created by the plasmin enzyme being activated. This implies that there is degraded fibrin in the bloodstream. The D-dimer represents the activity of the coagulation and fibrinolysis systems (10). Technically, the amount of D-dimer in the body is measured using a monoclonal antibody and a variety of commercial tests. To rule out deep vein thrombosis (DVT), pulmonary embolism (PE), and to establish the diagnosis of disseminated intravascular coagulation (DIC), the D-dimer test proved crucial in clinical examinations (11). Nearly all patients with severe venous thromboembolism experience the D-dimer levels was increased (VTE). High D-dimer levels can be found in pathological conditions including cancer, inflammation, and surgery as well as physiological conditions like pregnancy (12). D-dimer kit sensitivity ranges from one manufacturer to the next, with findings between 93% and 95%. (13). Additionally, numerous studies have demonstrated that COVID-19 puts people at risk for thrombosis in both veins and arteries (14). Because of this, people with COVID-19 had a 25% greater risk of DVT, VTE, and perhaps PE (15). In COVID-19, severe inflammation (cytokine, endothelial, and macrophage activations), diffuse intravascular coagulation, immobility, and hypoxia because of considerable lung injury can all lead to VTE episodes (16). The D-dimer, lactate dehydrogenase was increased, the changing in ptt and pt were minor to nonexistent, and higher levels of antiphospholipid antibodies were all linked to corona infection (17).

The evidence for many specific immunity system cytokines affecting COVID-19 susceptibility is limited. (18), Although interleukin 6 modulation can be a successful therapeutic. However, a genetic variation that affects the immune response to interferon gamma (IFN) causes extremely severe disease when specific pathogens, such as tuberculosis-causing mycobacteria, are encountered (19), COVID-19 has also been determined to be important (20). In 2003, IFN was related with the raised risk of severe acute respiratory syndrome (SARS) (21). Functional study of SARS-CoV-2 proteins, on the other hand, reveals that the virus is susceptible to IFN (22). These findings show that IFN or its antecedents, such as interleukin-18, may play a role in inflammation (23), COVID-19 may be influenced by interleukin-12 or interleukin-23. IL-18 has been proposed as a possible intervention target in COVID-19 (24). Interleukin-18's importance in immune function is further supported by its role in various autoimmune illnesses (including inflammatory bowel disease and eczema-dermatitis) (25).

MATERIALS AND METHODS

Subjects and blood sample collection

From March 15th to August 2022, this study was conducted at Al-Yarmouk Teaching Hospital. This research was done on the Covid-19 group, This includes 45 patients, aged between (40-65)of both sexes , The control group apparently consists of 45 healthy individuals. After collecting the serum, we divided it into several parts to perform tests on lipid profiles (TC, TG, HDL, and LDL), kidney function parameters (urea and creatinine), D-dimer levels, NF-, TGF, IL-12, and IL-18, and other measurements..

Body mass index (BMI) was computed by dividing the subjects' weight in kilograms by

their height in meters (m2). BMI is computed as follows (26):

BMI= weirht (kg)/(high (m))2

Biochemical analysis for Lipid profile tests by using an enzymatic method as specialized kits for each test for them. Friedewald's equation, an indirect simplified mathematical approach to estimating low-density lipoproteins, was used to calculate serum low-density lipoprotein-cholesterol (LDL-C). It only applie to TG levels of less than 400 mg/dL.

LDL-C = TC - [HDL-C + TAG/5].

The concentration of D-Dimer was measured quantitatively according to miniVIDAS auto analyzer, (bioMérieux Company) France.The INF-ᵞ, TGF and IL-18 concentrations were measured by the (Biosours) ELISA kit The information analyzed utilizing Factual bundle to social Sciences (SPSS) adaptation 25. the information introduced Similarly as mean , standard deviation What's more ranges. A level for p – esteem under 0. 01and 0.05 was acknowledged significant.

RESULT AND DISCUSSION

Table 1 displays the distribution of study groups by age, gender, and BMI. Study participants ranged in age from 20 to 55 years, with a mean age of 44.68 years and a standard deviation (SD) of 11.54 years, respectively. Participants were split evenly between men and women, with a gender ratio of 44.4% male and 55.5% female. Age and gender comparisons between research groups revealed no appreciable differences (P 0.05).

Gao et al., 2021, showed a strong interaction between BMI, age, and ethnicity, with younger persons having greater HR per kg/m2 over BMI 23 kg/m2 than older people. Age is the most significant factor for raising a person's COVID-19 mortality risk. (109 [95% confidence interval] 108-110] in the 20-39 age group versus 80-100 years versus 1 07 [1 06-1 08] versus 1 04 [1 04-105]) and Black individuals (107 [1 06–1 08] vs 1 04 [1 04– 105]). In those with type 2 diabetes, hypertension, and cardiovascular disease, COVID-19 related to a unit increase in BMI revealed a marginally lower risk of hospitalization and ICU admission than those without these morbidities (27).These results were mainly unaffected by other health issues, such as type 2 diabetes. COVID-19 related death risk per BMI unit is higher in the younger age groups and diminishes with age. Despite the fact that severe COVID-19 effects in young people are uncommon, the attributable risk was highest in people in their middle years (40–59 years). The huge sample size also, allowed for the evaluation of additional possible interactions. Despite the fact that the risks associated with a BMI were larger for those of Black ethnicity than for people of White ethnicity, they found no indication of a link between BMI and sex or Asian or Chinese ethnicity (27).

In a community-based cohort analysis, Williamson et al. (2020) found that those with high blood pressure or a diagnose of hypertensions had reduced chances of COVID-19 related death association with obesity than the general population (28) .

In younger age groups, fattness and presistent disease are important risk factors for in-hospitale dead people, with the conecting of presistent disease and obesity being mainly significant in those less than 50 . The public health depeding on this inference., vaccine schedules, and hospital clinical decision-making (29).

TABLE 1: Demographic characteristics between Patients and control groups.

Parameter	Patients No(45)	Control No(45)	P-Value
	Mean±SD	Mean±SD	
Sex (M/F)	(20/25) (44.44/55.55)%	(23/22) (51.11/48.88)%	/
Age (Years)	44.68±11.54	40.2±8.61	0.126

J Popul Ther Clin Pharmacol Vol 30(5):e515–e525; 03 March 2023.

High (cm)	169.24±5.19	168.03±5.53	0.181
Weight (Kg)	78.93±10.34	70.2±11.39	0.05*
BMI(Kg/m2)	28.80±3.38	24.80±3.46	0.05*

p0.05 indicates significance, whereas p0.01 indicates high significance.

Table 3 shows the comparison in Biochemical, The means of TC, TG, and LDL were all substantially higher in the sick group than in the control group of healthy individuals for all values of, TC , TG , LDL) were (184.33±19.77 versus 146±14.26 mg/dl, P= 0.01; 130.42±18.77 versus 92.53±26.59 , P= 0.01; 119.36±19.80 versus 75.12±17.23 mg/dl, P= 0.0 the lipid profile 1; respectively). the lipid profile are linked to severity with mortality in patient of COVID-19. As a result, the lipid profile can be utilized to determine the severity of COVID-19 and its prognosis.

TABLE 2: Patients' and control groups' lipid profiles were compared.

Parameters	Patients No(45)	Control No(45)	p-value
	Mean±SD	Mean±SD	
TC(mg/dl)	184.33±19.77	146±14.26	0.05*
TG(mg/dl)	130.42±18.77	92.53±26.59	0.05*
HDL-c (mg/dl)	40.88±2.41	55.36±3.35	0.05*
LDL-c (mg/dl)	119.36±19.80	75.12±17.23	0.05*

p0.05 indicates significance, whereas p0.01 indicates high significance

Patients may develop dyslipidemia as a result of viral infection-induced chronic inflammation, Lipid in viral life cycle the metabolisim was a cheefed role on it. This process includes replication, membrane homeostasis, endocytosis, and exocytosis. (30). To tell the truth, after recovery, a prior SARS-CoV-1 infection causes abnormal lipid metabolism, indicating a biological connection. (31). Clinical findings showed that patients with acute Epstein-Barr virus (EBV) infection had lower HDL-C, TC, and LDL-C levels than their controls. (32). Many studies discovered the Hepatitis B patients had lower levels of HDL-C and LDL-C throughout the stage of cirrhosis (33). likewise, patients infected with the human immunodeficiency virus (HIV) showed lower HDL-C and TC, as well as greater TG, in comparison to HIV-free controls (34). A study found a connection between CMV infection and decresed values of HDL-C in women of tipical weight (35). The severity of dengue fever was found to be inversely and significantly associated to circulating TC and LDL-C by Lima et al. in a comprehensive anlysis and meta-analysis of many studies involving one thousand fifty three participants (36). In the International Monitoring Dialysis Outcomes (MONDO) experiment, lipid levels were discovered to be inversely related to both infection everyone effectes death (37). In persons with severe acute respiratory syndrome, dyslipidemia is infrequent (SARS). According to one study, SARS patients had lower total cholesterol levels compared to healthy controls (37). Another study found that 12 years after SARS infection, the lipid metabolism of recovered SARS patients had changed. (38). These results suggest that dyslipidemia may develop in patients with coronavirus-related illnesses. The fundamental cause of the decline in TC, HDL-C, and LDL-C readings in patients with severe COVID-19, however, is unknown. There have been several options put out in this regard. First off, in metabolism of lipid the liver was involved, SARS-CoV-2 has the potential to harm it, impairing the absorption and synthesis of lipoproteins. Inflammation has been shown to influence the hepatic apolipoprotein A-I gene's

expression. (39), It increases the pro-inflammatory serum amyloid protein A (SAA) binding, which lowers and displaces ApoA-I levels in HDL (40). It was discovered that SAA-loaded HDL particles cleared the bloodstream more quickly than regular HDL particles. The decresed of lecithin cholesterol acyltransferase (LCAT) in an inflammatory situation can reduce badly inflammatory response with HDL use. (41). Third, because of the virus's inflammatory response, vascular permeability may be affected, allowing cholesterol molecules to enter tissues like alveolar gaps and create exudates. Exudates include large amounts of protein and cholesterol (42). SARS patients' lungs and those of cynomolgus macaques that have the SARS-COV infection can both exhibit exudates (43), as do the premature phases of the lung disease of COVID-19 (44). Fourth, viral infection induces host cells to produce more free radicals (45), In COVID-19 individuals, this could hasten lipid breakdown. Fifth, decreased LDL-C levels may higher LDL absorption when IL-6 generated by immunocytes activated LDL receptor expression in hepatocytes, resulting in greater LDL absorption (46). Finally, because cholesterol is produced primarily through the diet, COVID-19's hypocholesterolemia could be linked to starvation. (47). A recent study found that COVID-19 patients' nutritional status has deteriorated, as seen by consistently lower albumin levels in the extreme Patients with COVID-19 (48). The concentrations of HDL-C and LDL-C gradually increased after recovery from COVID-19. (49), This could be owing to the fact that the patient's condition has improved. In addition, TC, HDL-C, and LDL-C values were lower in individuals who did not survive upon hospital admission and persisted until death (50).

Results of renal function compression between the covid-19 and control groups (Urea and Creatinine are presented in Table 3). Mean values of urea and creatinine in the patient group were considerably higher than those in the control group of healthy individuals. The biggest significant differences were in the values of(urea and creatinine) were (68.15±4.31 versus 30.9±1.90 mg/dl, P= 0.01; 1.11±0.10 versus 0.71±0.07 , P= 0.01; respectively).

TABLE 3: Kidney Function Test measured between Patients and control groups.

Parameters	Patients No(45) Mean±SD	Control No(45) Mean±SD	p-value
Urea (mg/dl)	68.15±4.31	30.9±1.90	0.01*
Creatinine (mg/dl)	1.11±0.10	0.71±0.07	0.05**

p0.05 indicates significance, whereas p0.01 indicates high significance.

On admission, COVID-19 patients had a significant rate of early kidney function impairment. Clinicians may be able to identify patients with a bad prognosis if they have early kidney injury.

In the study of Xia et al. (2021), In COVID-19 individuals, a substantial relationship was shown between early renal function damage and poor outcomes (51).

As a result of the SARS-CoV-2 virus propagated primarily with signs of viral pneumonia, across the respiratory airway being the most common and initial symptom, Clinicians have concentrated on a lot of awareness on pneumonia treatment.

But the quantity of ACE2 expression in the kidney, namely in the renal tubules comparable to that in the lung, indicating that the kidney may some other significant organ for SARS-CoV-2 to infect (52). Proof from the Middle East respiratory syndrome coronavirus (MERS-CoV) suggests that SARS-CoV-2 may directly strike renal tubular epithelial cells (53). SARS-CoV-2 granules have been found in the urine of patients. Autopsy electron micrographs of kidneys revealed viral particles, confirming theory of a direct viral attack in kidneys. (54). Despite the

fact that the mechanism of SARS-CoV-2 kidney injury is still unknown, In order to fully investigate these issues, more research is required.

In the present study showed that D-dimer in (ng/ml) for covid-19 patients was (581.82±78.21)ng/ml, while foe control group was (194.63±18.11)ng/ml , a highly significant differences ($p<0.0001$) was found between patients and control groups as showed in table 4.

TABLE 4: D-Dimer Test measured between Patients and control groups.

Parameters	Patients No(45)	Control No(45)	p-value
	Mean±SD	Mean±SD	
D-Dimer (ng/ml)	581.82±78.21	194.63±18.11	0.0001***

p0.05 indicates significance, whereas p0.01 indicates high significance.

The relationship between increased D-dimer levels and COVID-19 disease severity was investigated in this study in patients was analyzed and comparison with control. COVID-19 patients had higher D-dimer levels, according to the study. and this agree with (55) which showed that very high D-dimer levels are common in COVID-19 pneumonia and correlate with a worse prognosis. In the lungs, the inflammatory response results in small vessel endothelialitis, which sets off the clotting cascade and produces microvascular and macrovascular thrombosis (56). In COVID-19 patients, scientists discovered anomalies in the vascular endothelium, changed blood flow, and platelet dysfunction, all of which led to repeated thromboses , The clinical development of COVID-19 has been linked to aberrant coagulation function, particularly high D-dimer levels., These findings are helpful in the early detection and treatment of serious disease (57).

Table 5 showed the comparison between patients and control group according some anti-inflammation parameters such as ((INF-ɣ, TGF , IL-12 and IL-18) the results found that mean of them as (7.30±1.21 versus 36.66±5.44; $p<0.001$; 35.18±8.80 versus 100.13±16.73 , P= 0.001; 56.91±9.17 versus 14.76±4.12 , P= 0.001 ; 385.44±29.05 versus 126.93±14.32, P= 0.001 ; respectively).

The present study found that the control group was higher levels in INF-ɣ and TGF than the patients group with highly significant decreased (P= 0.001), while the levels of other parameters (IL-12 and IL-18) were higher significant increased in patients group than in control group with (P= 0.001).

One of the most common side effects of SARS-CoV-2 infection is pulmonary fibrosis (58). SARS-CoV-2 is an RNA virus with an envelope. that causes severe pneumonia symptoms and is closely linked to SARS-CoV and MERS-CoV (59). The virus is transferred through respiratory droplets, close contact, and other means, and asymptomatic people may unintentionally infect others (60). According to current evidence, SARS-CoV-2 has a lesser pathophysiology than SARS but a more strong transmission competence. Both the ACE2 receptor and the S protein priming serine protease TMPRSS2 are abundantly expressed in respiratory epithelial cells and are essential for its entrance into target cells (61).

TABLE 5: Anti-Inflammation parameters measured between Patients and control groups.

Parameters	Patients No(45) Mean±SD	Control No(45) Mean±SD	p-value
INF-ɣ (ng/ml)	7.30±1.21	36.66±5.44	0.001**
TGF (ng/ml)	35.18±8.80	100.13±16.73	0.001**
IL-12 (ng/ml)	56.91±9.17	14.76±4.12	0.001**
IL-18(ng/ml)	385.44±29.05	126.93±14.32	0.001**

p0.05 indicates significance, whereas p0.01 indicates high significance.

Following infection, infected cells secrete a large amount of chemokines and cytokines, resulting in cytokine storm. ARDS, severe pneumonia, and inflammatory-induced lung injury can all be brought on by a cytokine storm that harms microvascular endothelial cells, ischemia, and hypoxia in addition to lung epithelial cells (62). If the cytokine storm is not cleared promptly, the lung tissue will be damaged, which will result in pulmonary fibrosis. TGF is a cytokine with anti-inflammatory properties that is important in acute lung injury. One of the most crucial areas for anti-fibrotic treatment is its route (63).The goal of Hu et al(2020) .'s study was to see if there was a link between pulmonary fibrosis and pro-inflammatory cytokines in COVID-19 patients. They have not found a link between TGF-beta and lung fibrosis because TGF-beta is an anti-inflammatory cytokine. In COVID-19 patients, they discovered an inverse link between basal IFN- level and lung fibrosis at discharge. Lymphocytes, particularly T cells and NK cells, create IFN- when they are stimulated by specific antigens or mitogens. IFN- signaling is involved in a variety of cellular processed, including macrophage activation and host defense against pathogen infection. The increase in fibrosis volume in COVID-19 at discharge was inversely linked with baseline levels of IFN-. These findings imply that early antiviral infection utilizing IFN- may have a significant impact on fibrosis inhibition and functional recovery (64).

The major purpose of IL-12 is to promote cytolytic activity and IFN production by NK cells and T cells (65). IL-12-independent T-cell activation and IFN- release have been observed after a number of viral infections, including infection with the systemic lymphocytic choriomeningitis virus (66) and a respiratory tract infection brought on by the influenza virus (67). This may be the case because type I IFN stimulates the release of IFN by cells (68).

Interleukin-18 is thought to perform a wide range of roles in infection defense (69). Interleukin-18's role in lowering the incidence of COVID-19 is only supported by observational studies (70)

Interleukin-18 is difficult to interpret in observational studies of patients since it may represent a protective response, a symptom, or the root of problems. As far as we are aware, there is no experimental proof of interleukin-18's involvement with COVID-19. Experimental data, however, suggest that interleukin-18 also works with other viruses. It has been shown that interleukin-18, in particular, prevents mice from dying from herpes simplex 1 (71), possibly through the action of natural killer cells (70) or IFN (72). Interferon (IFN)-mediated inhibition of viral replication by IL-18 has also been shown to protect mice against the murine coronavirus mouse hepatitis virus strain A59, although IL-1 was not (73). Rats have also been shown to be protected from the rotavirus by IL-18, possibly through caspase-inducing apoptosis.(74), As a result, it's been recommended as a possible way to deal with new and stubborn viruses (75). Interleukin-18's ability to guard against infection is consistent with it raising the likelihood of auto-immunity and atopic diseases (76), IL-18 also reduced the number of children, confirming the duplication and continuity are mutually exclusive.. COVID-19 may be protected by nterleukin-18. COVID-19 could be a result of the immune system's initial failure. It's possible that recombinant interleukin-18 could prevent some of these failures (77).

CONCLUSION

The present study concludes that Covid-19 cause alteration in lipid profile, kidney functions, D-dimer and some anti- inflammatory parameters.

REFERENCES

1. D Benvenuto, M Giovanetti, A Ciccozzi, S Spoto, S Angeletti, M. Ciccozzi, (2020). The 2019-new coronavirus epidemic: evidence for virus evolution J Med Virol, 92, 455-459
2. M Abu-Farha, TA Thanaraj, MG Qaddoumi, A Hashem, J Abubaker, F. Al-Mulla , (2020). The role of lipid metabolism in COVID-19 virus infection and as a drug target Int J Mol Sci, 21, 3544.
3. E Kocar, T Rezen, D. Rozman , (2021). Cholesterol, lipoproteins, and COVID-19: basic concepts and clinical applications Biochim Biophys Acta Mol Cell Biol Lipids, 1866, Article 158849
4. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al. (2008). Aspects of immune dysfunction in end-stage renal disease. Clinical journal of the American Society of Nephrology: CJASN.;3(5):1526–33. pmid:18701615
5. Chou CY, Wang SM, Liang CC, Chang CT, Liu JH, Wang IK, et al. ,(2014). Risk of pneumonia among patients with chronic kidney disease in outpatient and inpatient settings: a nationwide population-based study. Medicine.;93(27): 174.
6. Henry BM, Lippi G., (2020) .Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. International urology and nephrology.;52(6):1193–4.
7. Chen YT, Shao SC, Lai EC, Hung MJ, Chen YC., (2020).Mortality rate of acute kidney injury in SARS, MERS, and COVID-19 infection: a systematic review and meta-analysis. Critical care. 24(1):439.
8. Gaffney PJ. (1980). Breakdown products of fibrin and fibrinogen: molecular mechanisms and clinical implications. J Clin Pathol.;14:10–17.
9. Halaby R, Popma CJ, Cohen A, et al., (2015). D-Dimer elevation and adverse outcomes. J Thromb Thromboly.;39(1):55–59.
10. De Monyé W, Sanson BJ, Mac Gillavry MR, et al., (2002). Embolus location affects the sensitivity of a rapid quantitative D-dimer assay in the diagnosis of pulmonary embolism. J Respir Crit Care Med.;165(3):345–348.
11. Schrecengost JE, LeGallo RD, Boyd JC, et al. (2003). Comparison of diagnostic accuracies in outpatients and hospitalized patients of D-dimer testing for the evaluation of suspected pulmonary embolism. Clin Chem.;49(9):1483–1490.
12. Cui S, Chen S, Li X, et al. (2020). Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost.;18(6):1421–1424.
13. Zhang L, Feng X, Zhang D, et al. (2020). Deep vein thrombosis in hospitalized patients with coronavirus disease (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome. Circulation.;142(2):114–128.
14. Klok FA, Kruip M, van der Meer NJM, et al , (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res.;191:145–147.
15. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020;382(17):e38.
16. Li, M, Yeung, CHC and Schooling, CM ,(2021) .Circulating cytokines and coronavirus disease: a Bi-directional Mendelian randomization study. Frontiers in Genetics 12, 680646.
17. Kerner, G et al. (2021) Human ancient DNA analyses reveal the high burden of tuberculosis in Europeans over the last 2,000 years. American Journal of Human Genetics 108, 517–524.
18. The COVID-19 Host Genetics Initiative AG (2021) Mapping the human genetic architecture of COVID-19 by worldwide meta-analysis. medRxiv.
19. Lau, YL and Peiris, JS (2009). Association of cytokine and chemokine gene polymorphisms with severe acute respiratory syndrome. Hong Kong Medical Journal 15, 43–46.
20. Hayn, M et al. (2021) Systematic functional analysis of SARS-CoV-2 proteins uncovers viral innate immune antagonists and remaining vulnerabilities. Cell Reports 35, 109126.
21. Kaplanski, G (2018) Interleukin-18: biological properties and role in disease pathogenesis. Immunological Reviews 281, 138–153.
22. Vecchié, A et al. (2021) IL-18 and infections: is there a role for targeted therapies? Journal of Cellular Physiology 236, 1638–1657.
23. McGowan, LM et al. (2019) Integrating Mendelian randomization and multiple-trait colocalization to uncover cell-specific inflammatory drivers of autoimmune and atopic disease. Human Molecular Genetics 28, 3293–3300.
24. Simon C., Everitt H. & Kendrick T. (2005) Oxford Handbook of General Practice. 2nd Edition. Oxford University Press. Pp. 712-728.
25. Richmond W. (1992). Analytical reviews in clinical biochemistry: the quantitative analysis of cholesterol. Ann. Clin.Biochem. 29(26):577-597.
26. Larsen ,K.Clin.Chim. (1972) Acta.41:204.
27. Min Gao,Carmen Piernas, Astbury , Julia Hippisley-Cox, (2021), Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective,

community-based, cohort study, FRCP , 9(6): 350-359.
28. Williamson EJ, Walker AJ , Bhaskaran K, et al. (2020) , Factors associated with COVID-19-related death using OpenSAFELY. Nature.; 584: 430-436.
29. Yates, T., Zaccardi, F., Islam, N. et al. (2021), Obesity, chronic disease, age, and in-hospital mortality in patients with covid-19: analysis of ISARIC clinical characterisation protocol UK cohort. BMC Infect Dis 21, 717.
30. Abu-Farha M., Thanaraj T.A., Qaddoumi M.G., Hashem A., Abubaker J., Al-Mulla F. (2020), The role of lipid metabolism in COVID-19 virus infection and as a drug target. Int J Mol Sci. 17; 21: 3544.
31. Wu Q., Zhou L., Sun X., Yan Z., Hu C., Wu J., et al.(2017), Altered lipid metabolism in recovered SARS patients twelve years after infection. Sci Rep. 22; 7: 9110
32. Apostolou F., Gazi I.F., Lagos K., Tellis C.C., Tselepis A.D., Liberopoulos E.N., et al. (2010). Acute infection with Epstein-Barr virus is associated with atherogenic lipid changes, Atherosclerosis ; 212: 607-613
33. Cao W.J., Wang T.T., Gao Y.F., Wang Y.Q., Bao T., Zou G.Z.(2019) Serum lipid metabolic derangement is associated with disease progression during chronic HBV infection. Clin Lab.1; 65
34. Baker J. Ayenew W. Quick H., Hullsiek K.H., Tracy R., Henry K., et al. (2010), High-density lipoprotein particles and markers of inflammation and thrombotic activity in patients with untreated HIV infection., J Infect Dis.15; 201: 285-292
35. Fleck-Derderian S., McClellan W., Wojcicki J.M. (2017), The association between cytomegalovirus infection, obesity, and metabolic syndrome in U.S. adult females. Obesity (Silver Spring); 25: 626-633
36. Lima W.G., Souza N.A., Fernandes S.O.A., Cardoso V.N., Godói I.P. (2019), Serum lipid profile as a predictor of dengue severity: a systematic review and meta-analysis. Rev Med Virol.; 29e2056
37. Kaysen G.A., Ye X., Raimann J.G., Wang Y., Topping A., Usvyat L.A., et al. (2018), Lipid levels are inversely associated with infectious and all-cause mortality: international MONDO study results. J Lipid.
38. Song S.Z., Liu H.Y., Shen H., Yuan B., Dong Z.N., Jia X.W., et al.(2004). Comparison of serum biochemical features between SARS and other viral pneumonias. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue.; 16: 664-666.
39. Han C.Y., Chiba T., Campbell J.S., Fausto N., Chaisson M., Orasanu G., et al., (2006). Reciprocal and coordinate regulation of serum amyloid A versus apolipoprotein A-I and paraoxonase-1 by inflammation in murine hepatocytes., Arterioscler Thromb Vasc Biol.; 26: 1806-1813.
40. Han C.Y., Tang C.,Guevara M.E., Wei H., Wietecha T., Shao B., et al., (2016). Serum amyloid A impairs the antiinflammatory properties of HDL., J Clin Invest.; 126: 266-281
41. Khovidhunkit W., Shigenaga J.K., Moser A.H., Feingold K.R., Grunfeld C., (2001). Cholesterol efflux by acute-phase high density lipoprotein: role of lecithin: cholesterol acyltransferase., J Lipid Res.; 42: 967-975
42. Light R.W. Macgregor M.I., Luchsinger P.C.,Ball Jr., W.C., (1972). Pleural effusions: the diagnostic, separation of transudates and exudates., Ann Intern Med.; 77: 507-513.
43. Hwang D.M., Chamberlain D.W., Poutanen S.M., Low D.E., Asa S.L., Butany J., (2005). Pulmonary pathology of severe acute respiratory syndrome in Toronto., Mod Pathol.; 18: 1-10
44. Pei F., Zheng J., Gao Z.F., Zhong Y.F., Fang W.G.. Gong E.C.. et al. (2005). Lung pathology and pathogenesis of severe acute respiratory syndrome: a report of six full autopsies. Zhonghua Bing Li Xue Za Zhi.; 34 (PMID: 16536279): 656-660.
45. Tian S., Hu W., Niu L., Liu H., Xu H., Xiao S.Y. (2020). Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer., J Thorac Oncol.; 15: 700-704
46. Zidar D.A., Juchnowski S.,Ferrari B., Clagett B., Pilch-Cooper H.A., Rose S., et al.,(2015). Oxidized LDL levels are increased in HIV infection and may drive monocyte activation.. J Acquir Immune Defic Syndr. 1; 69: 154-160
47. Gierens H., Nauck M., Roth M., Schinker R., Schürmann C., Scharnagl H., et al.,(2000). Interleukin-6 stimulates LDL receptor gene expression via activation of sterol-responsive and Sp1 binding elements., Arterioscler Thromb Vasc Biol.; 20: 1777-1783
48. Chiarla C., Giovannini I., Giuliante F., Zadak Z., Vellone M., Ardito F., et al. (2010). Severe hypocholesterolemia in surgical patients, sepsis, and critical illness., J Crit Care ; 25 (361.e7-361.e12)
49. Sun J.T., Chen Z., Nie P., Ge H., Shen L., Yang F., et al., (2020). Lipid profile features and their associations with disease severity and mortality in patients with COVID-19. Front Cardiovasc Med.; 7: 584987
50. Tanaka S., De Tymowski C., Assadi M., Zappella N., Jean-Baptiste S., Robert T., et al. (2020). Lipoprotein concentrations over time in the intensive care unit COVID-19 patients: results from the ApoCOVID study. PloS One.; 15 ,0239573.
51. Xia, T., Zhang, W., Xu, Y. et al. (2021). Early

kidney injury predicts disease progression in patients with COVID-19: a cohort study. BMC Infect Dis 21, 1012.
52. Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. (2020). Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med.;46:1114–6.
53. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. (2020). SARS-CoV-2, SARS-CoV, and MERS-COV: a comparative overview. Infez Med.;28:174–84.
54. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al (2020). Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int.;98:219–27.
55. Mohsen and Al-Mossawi , (2021). Dynamic relationship between D-dimer and COVID-19 severity, A report Submitted to the Council of Institute of Genetic Engineering and Biotechnology for Post Graduate Studies – University of Baghdad as a Partial Fulfillment of the Requirements for the Degree of Higher Diploma in Genetic Engineering and Biotechnology.
56. Ackermann, M.; Verleden, S. E.; Kuehnel, M.; Haverich, A.; Welte, T.; Laenger, F. et al. (2020). Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. New England Journal of Medicine, 383(2):120-128.
57. Han, H.; Yang, L.; Liu, R.; Liu, F.; Wu, K. L.; Li, J. et al. (2020). Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clinical Chemistry and Laboratory Medicine (CCLM), 58(7): 1116-1120.
58. Xiaoneng MO, Wenhua J, Zhuquan S, Mu C, Hui P, Ping P, et al. (2020). Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 55:2001217
59. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen, E. . (2020). COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect26:729–34.
60. Netea MG, Giamarellos-Bourboulis EJ, Domínguez-Andrés J, Curtis N, van Crevel R, van de Veerdonk FL, et al. (2020). Trained immunity: a tool for reducing susceptibility to and the severity of SARS-CoV-2 infection. Cell. 181:969–77.
61. Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova M, et al. . (2020). SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med: 26:681–7.
62. Cao, X. COVID-19: (2020) . Immunopathology and its implications for therapy. Nat Rev Immunol. 20:269–70.
63. Meng XM, Nikolic-Paterson DJ, Lan, HY. TGF-β: (2016) the master regulator of fibrosis. Nat Rev Nephrol. 12:325–38.
64. Hu ZJ, Xu J, Yin JM, Li L, Hou W, Zhang LL, Zhou Z, Yu YZ, Li HJ, Feng YM and Jin RH (2020) Lower Circulating Interferon-Gamma Is a Risk Factor for Lung Fibrosis in COVID-19 Patients. Front. Immunol. 11:585647.
65. Trinchieri, G.(2003). Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat. Rev. Immunol.3:133-146.
66. Orange, J. S., and C. A. Biron.(1996). An absolute and restricted requirement for IL-12 in natural killer cell IFN-gamma production and antiviral defense: studies of natural killer and T-cell responses in contrasting viral infections. J. Immunol.156:1138-1142.
67. Monteiro, J. M., C. Harvey, and G. Trinchieri.(1998). Role of interleukin-12 in primary influenza virus infection. J. Virol.72:4825-4831.
68. Cousens, L. P., R. Peterson, S. Hsu, A. Dorner, J. D. Altman, R. Ahmed, and C. A. Biron.(1999). Two roads diverged: interferon alpha/beta- and interleukin 12-mediated pathways in promoting T-cell interferon gamma responses during viral infection. J. Exp. Med.189:1315-1328.
69. Galván-Peña S et al. (2021) Profound treg perturbations correlate with COVID-19 severity. Proceedings of the National Academy of Sciences of the USA 118, , 2111315118.
70. Zhang Y et al. (2021) Identification of monocytes associated with severe COVID-19 in the PBMCs of severely infected patients through single-cell transcriptome sequencing. Engineering (Beijing). PubMed
71. Fujioka N et al. (1999) Interleukin-18 protects mice against acute herpes simplex virus type 1 infection. Journal of Virology 73, 2401–2409.
72. Barr DP et al. (2007) A role for plasmacytoid dendritic cells in the rapid IL-18-dependent activation of NK cells following HSV-1 infection. European Journal of Immunology 37, 1334–1342.
73. Reading PC et al. (2007) IL-18, but not IL-12, regulates NK cell activity following intranasal herpes simplex virus type 1 infection. The Journal of Immunology 179, 3214–3221.
74. Zalinger ZB, Elliott R and Weiss SR (2017) Role of the inflammasome-related cytokines Il-1 and Il-18 during infection with murine coronavirus. Journal of NeuroVirology 23, 845–854.
75. Zhang B et al. (2014) Viral infection. Prevention and cure of rotavirus infection via TLR5/NLRC4-mediated production of IL-22 and IL-18. Science (New York, NY) 346, 861–865.
76. McGowan LM et al. (2019) Integrating Mendelian randomization and multiple-trait colocalization to uncover cell-specific inflammatory drivers of autoimmune and atopic

disease. Human Molecular Genetics 28, 3293–3300.
77. Yeung, S. L. (2021). Interleukin-18 and COVID-19. Epidemiology and infection, 150, e14.