Investigating od some Lab parameters in Covid-19 patients in Kirkuk City-Iraq before and weeks after IL-6 antagonist therapy, a short prospective, observational study

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Abstract

Background: Interleukin-6 receptor antagonists (IL-6RAs) and steroids are emerging immunomodulatory therapies for severe and critical coronavirus disease (COVID-19). In this preliminary report, we aim to describe the epidemiology, clinical characteristics, and outcomes of adult critically ill COVID-19 patients,

Aim: to evaluate whether the immunomodulation with an IL-6 antagonist is associated with an improved hemostasis in patients with COVID-19 as measured by viscoelastic tests.

Materials and methods: This prospective study was conducted in Kirkuk city – Iraq, from the first of March 2021 until the end of June 2021. The study included 50 patients from both sexes with age above (18-60) years. Clinical and laboratory parameters, such as blood pressure (systolic, diastolic), heart rate, peripheral capillary oxygen saturation (SpO2), respiratory rate, body temperature, disease severity scores, ventilation parameters, blood gas parameters, VHA results will be recorded at set time intervals (see later). All the medication that the patient has taken during the study period will be noted. Blood culture samples will also be taken when indicated to exclude superinfection thus ensuring that these will not influence the results of the study. Blood sample was collected by vein puncture from each subject enrolled in this study . for determination of ALT, AST, LDH , S. creatinine, BUN , TSB and S . Albumin . The primary outcome is the change of the Lab parameters measured   before IL-6 antagonist and 2 weeks after immunomodulation therapy of IL-6 antagonist. As and the effect of it are relatively shortly seen in inflammatory parameters after administration, we decided to use the parameters. In addition, the study will investigate the following secondary outcomes

Results: The study revealed that, the risk of covid-19 infection increased with age as elderly was most affected. The study showed that 36.36% of covid-19 smoker cases were with severe infection, 27.27% were with critical infection and 18.18% were with moderate infection (P<0.001). The study demonstrated that,   74% (37 0f 50) of covid-19 infected patients improved after two weeks of infection 22% had complication of infection while unfortunately, 4% (3 of 50) died due to complications of Covid-19 infection. The study showed that random blood sugar was relatively high in COVID-19 patients (213.4±60.14) mg/dL and then decreased slightly two weeks after treatment (174.9±49.9) mg/dL compared to the control group (105.7 ±15.9) (P:0.001), andthe highest rate of D-Dimer testing was recorded in COVID-19 patients

(760.3±187). 8 ng/ml and then decreased slightly two weeks after treatment (167.3±657.9 ng/ml compared to the control group (105.7±15.9). The study also showed that the highest rate of lactate dehydrogenase (LDH) was recorded in COVID-19 patients (348.6±65.7) U/L and then relatively decreased after two weeks of treatment (315.3±60.4) U/L compared to the control group (96.7±23.9) U/L. The study showed that the highest levels of ferritin were recorded in COVID-19 patients (390.4±83.5) ng/ml and then relatively low two weeks after treatment (319.5±81). 3)ng/ml, compared to the control group (96.7±23.9)ng/ml. The study also revealed that the highest levels of urea, creatinine and ALT were recorded in patients with Covid- and then its rate decreased relatively two weeks after receiving treatment, compared to a group. While the study revealed that the rate of albumin was significantly low in COVID-19 patients and then increased relatively after two weeks of receiving compared to the control group who were characterized by a normal rate of albumin. TCZ appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms. And for these critically ill patients with elevated IL-6, the repeated dose of the TCZ is recommended.

Keywords: COVID-19; IL-6 antagonist; LDH; Ferritin; D-dimer

Introduction

The emerging SARS-CoV-2 virus has shed new light on the cross-talk between the immune and the blood coagulation system. From the pathophysiological standpoint in COVID-19 infection, the thrombo-inflammatory process is initiated by the host's exaggerated systemic inflammatory response, also called 'dysregulated immune response' that activates both the inflammatory and the coagulation cascade directly by inflammatory mediators and indirectly by causing endothelial cell injury [1]. These mechanisms altogether contribute to the imbalance of the haemostasis that is characterised by a procoagulant state that is characterised by increased number of thrombotic complications even despite the implementation of thromboprophylaxis[2]. Patients suffered from cytokine storms progress to cardiovascular collapse, multiple organ dysfunction, and death rapidly. Therefore, early identification, treatment, and prevention of the cytokine storms are of crucial importance for the patients. [3]. The lower mortality rate was more marked among patients who received concomitant steroids and did not require invasive mechanical ventilation (iMV) at randomization. As such, WHO Living guideline recommends IL-6RAs (tocilizumab or sarilumab) in combination with steroids for patients with severe or critical COVID-19 [4]. Moreover, the Bayesian reanalysis of RECOVERY trial showed that hospitalized COVID-19 patients on non-invasive ventilation (NIV), and high-flow nasal cannula (HFNC) have a high probability of a clinically meaningful outcome benefit from tocilizumab [5,6]. Therefore, the immunomodulatory effect of IL6-RAs appears to be most beneficial in combination with steroids and when administered in the early phase of critical care trajectory.In an experimental study on healthy volunteers, IL-6—among other cytokines—was added to the blood and the changes caused by the cytokine in the blood coagulation were evaluated by using viscoelastic haemostasis assay (VHA) [7,8]. As the effect of IL-6 administration, a fragile, unstable clot was formed quicker than in the healthy volunteers' blood prior to the addition of the cytokine. Furthermore, a proteomic study showed that very high levels of IL-6 can increase the level of SERPIN and CPB2/TAF carboxypeptidases that have an inhibitory effect on fibrinolysis[9]. IL-

6 antagonists were introduced in the guidelines of COVID-19 treatment in case of severely ill patients with increased need for oxygen support, like high-flow nasal oxygen therapy, non-invasive or invasive mechanical ventilation[10,11]. According to the current literature, few studies have evaluated the changes that this therapy caused in the immune response and the crosstalk between the blood coagulation system by using viscoelastic haemostatic assays in patients with COVID-19 [12]. Therefore, this study could provide further data on this topic. We aim to evaluate whether the immunomodulation with an IL-6 antagonist is associated with an improved haemostasis in patients with COVID-19 as measured by viscoelastic tests.

Materials, and Methods

This prospective study was conducted in Kirkuk city – Iraq, from the first of March 2021 until the end of June 2021. The study included 50 patients from both sexes with age above (18-60) years. The protocol for this study was approved by Directorate of Kirkuk Health. Each patient was educated about the research, filled out a questionnaire, and signed a consent form to participate in the study.

Exclusion criteria:

1- Chronic liver and renal disease.
2- Any medicines that may alter patients finding like steroid, NSAID drugs, diuretics, chemotherapy.

Clinical and laboratory parameters, such as blood pressure (systolic, diastolic), heart rate, peripheral capillary oxygen saturation (SpO2), respiratory rate, body temperature, disease severity scores, ventilation parameters, blood gas parameters, VHA results will be recorded at set time intervals. All the medication that the patient has taken during the study period will be noted. Blood culture samples will also be taken when indicated to exclude superinfection thus ensuring that these will not influence the results of the study.

Data entry of the variables of interest will be performed by the investigators at the participating sites using a web-based database. All participating sites will use the same electronic case report forms. The patients will receive a unique identifier to anonymise their data.

Tocilizumab can be used as a treatment with different doses for patients with severe cases and an increased level of IL-6, and those who have extensive lung lesions. The doses start from an initial 4-8 g/kg with more than one hour of infusion into the body. One extra dose can be given after 12 hours if the first dose is not effective. Attention should be paid not to use more than two administrations with a single dose of 800 mg, allergic reaction, and administration to patients with an active infection, such as tuberculosis

Five ml of blood sample was collected by vein puncture from each subject enrolled in this study .Blood samples were placed into sterile gel tube tubes, after blood clotting, centrifuged at 3000 rpm for 15 minute then serum removed and transferred into Tow Eppendorf tubes which labelled and kept at -20 C for determination of ALT, AST, LDH , S. creatinine, BUN , TSB and S . Albumin by using Cobase C311 analyzer.

The primary outcome is the change of the Lab parameters measured before IL-6 antagonist and 2 weeks after immunomodulation therapy of IL-6 antagonist. As and the effect of it are relatively

shortly seen in inflammatory parameters after administration, we decided to use the parameters. In addition, the study will investigate the following secondary outcomes

Results

The study revealed that, the risk of covid-19 infection increased with age as elderly was most affected. The study also found that males were more affected by the virus from females, Table 1

Table 1: Distribution of Covid-19 smoker patients according to age and sex

Variables	No.	%
Age (years)		
18-27	4	8
28-37	5	10
38-47	7	14
48-57	11	22
58-67	14	28
68-77	9	18
Total	50	100
Sex		
Females	22	44
Males	28	56
Total	50	100

The study showed that 40% of covid-19 cases were asymptomatic, 20% were with mild infection, 18% were with severe infection and 6% were with critical infection (P<0.001), Table 2

Table 2: Distribution of covid-19 patients according to clinical presentation

| Covid-19 cases	No.	%
Asymptomatic	20	40
Mild	10	20
Moderate	8	16
Severe	9	18
Critical	3	6
Total	50	100

P. value <0.001

The study showed that 36.36% of covid-19 smoker cases were with severe infection, 27.27% were with critical infection and 18.18% were with moderate infection (P<0.001), Table 3

Table 1: Distribution of covid-19 patients according to clinical presentation and smoking

Covid-19 cases	Total No.	Smoker	%
Asymptomatic	20	1	9.09
Mild	10	1	9.09
Moderate	8	2	18.18
Severe	9	4	36.36
Critical	3	3	27.27
Total	50	11	100

P. value <0.001

The study demonstrated that,   74% (37 0f 50) of covid-19 infected patients improved after two weeks of infection 22% had complication of infection while unfortunately, 4% (3 of 50) died due to complications of Covid-19 infection, Figure 1.
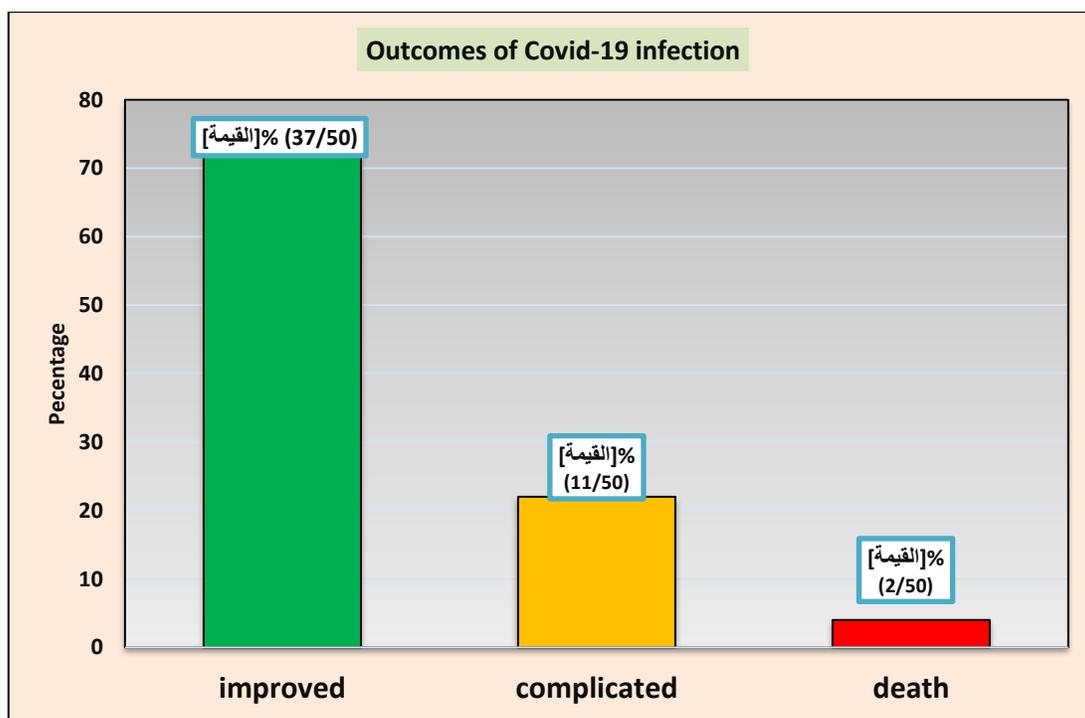
Figure 1: Distribution of Covid-19 infected patients according to outcomes of infection

The study showed as shown in Table 4-7. that random blood sugar was relatively high in COVID-19 patients   (213.4±60.14) mg/dL and   then decreased slightly two weeks after treatment (174.9±49.9) mg/dL compared to the control group (105.7 ±15.9) (P:0.001), andthe

highest rate of D-Dimer testing was recorded in COVID-19 patients (760.3±187). 8 ng/ml and then decreased slightly two weeks after treatment (167.3±657.9 ng/ml compared to the control group (105.7±15.9). The study also showed that the highest rate of lactate dehydrogenase (LDH) was recorded in COVID-19 patients (348.6±65.7) U/L and then relatively decreased after two weeks of treatment (315.3±60.4) U/L compared to the control group (96.7±23.9) U/L. The study showed that the highest levels of ferritin were recorded in COVID-19 patients (390.4±83.5) ng/ml and then relatively low two weeks after treatment (319.5±81). 3)ng/ml, compared to the control group (96.7±23.9)ng/ml. The study also revealed that the highest levels of urea, creatinine andALT were recorded in patients with Covid- and then its rate decreased relatively two weeks after receiving treatment, compared to a group. While the study revealed that the rate of albumin was significantly low in COVID-19 patients and then increased relatively after two weeks of receiving compared to the control group who were characterized by a normal rate of albumin, while the study revealed that There was no significant difference between the study groups in terms of ALP and AST averages as they were close within the study groups.

Table 4: **Mean of variables conducted in the study in COVID-19 patients before** and **after treatment and control group**

Variables (Mean±SD)	Study Groups		Control group (n:30)	P. value
	Covid-19 (n:50)			
	Before treatment	After treatment		
Blood sugar (mg/dL)	213.4±60.14	174.9±49.9	105.7±15.9	0.001
D-Dimer (ng/ml)	760.3±187.8	167.3±657.9	145.9±342.7	0.0001
LDH (U/L)	348.6±65.7	315.3±60.4	202.1±45.6	0.0001
Ferritin (ng/ml)	390.4±83.5	319.5±81.3	96.7±23.9	0.0001
Blood urea (mg /dL)	78.3±13.5	64.6±12.3	26.3±5.6	0.0001
Serum creatinine (mg /dL)	1.66±0.34	1.36±0.31	0.74±0.25	0.0001
Blood albumin (g /dL)	3.25±0.93	3.15±0.83	4.27±0.78	0.0001
ALT (unit/liter)	34.45±3.31	26.14±3.22	14.34±2.12	0.0001
AST (unit/liter)	27.44±2.47	25.75±3.12	15.31±1.18	0.074
ALP (unit/liter)	66.45±9.33	65.23±9.15	59.65±8.37	0.092

Discussion

In agreement with our finding, Al-Azzawy *et al* [11]. in Kirkuk city showed that, majority of patients were elderly and 62.5% of COVID-19 patients were males. A study from Baghdad also found that, majority of COVID-19 patients were above 50 years of old and most of them were males[12]. A study by Zhang *et al* [13]. reported that the highest prevalence of COVID-19 in China was observed in males aged 45–59 years. Moreover, the Peruga *et al* [14]. reported that the highest prevalence of COVID-19 infection was in males. Previous studies had been reported older age as an important independent predictor of mortality in both SARS and MERS infection [15,16]. A study in Lancet, conducted on 191 patients with COVID-19 from Wuhan, China during the first outbreak, found that the most patients (62%) were male gender and increased age was associated with COVID-19 increasing rate of infection [17]. Also, in Lancet, a study conducted in intensive care unit (ICU) of Wuhan, China on 52 critically ill patients found that, 52% were elderly patients (>60 years) and (67%) patients were men. Recent study on 41 patients who admitted to designated hospital, Jin Yintan hospital (Wuhan, China) reported that (39%) patients were aged 50–64 years, no children or adolescents were infected and most of them were men (73%) [18].

According to previous studies, the most important risk factors were age, gender, and co-existing diseases. A review study found that older people were more liable to get the infection than younger age groups. The mortality among males was significantly higher compared to females with no approval of susceptibility to infection among two genders. The presence of pre-existing and any condition that weakens the immune system can be a risk factor for infection with COVID-19 [10,15]. In agreement with our results, Al-Azzawy *et al* [11] showed that were asymptomatic, 44.17% of cases of COVID-19 patients were with mild infection and 10% were with severe infection (P<0.001). Most of the cases studied by Al Hijaj *et al* [19] were either asymptomatic (51.3%) or with mild condition (30.3%). Critical cases represented a small proportion (3.2%) and older age and travel history were significant predictors of both severe cases and higher case fatality.   Taher [20] from Wasit city estimated that, asymptomatic mild illness represented the majority of covid-19 patients.

Although smokers appear to be consistently underrepresented among patients with COVID-19, the link between smoking and clinical outcomes in these patients remains less clear.

Data have revealed that use of tobacco significantly increases the angiotensin converting enzyme expression, the binding receptor for corona virus, that could clarify the increased exposure to COVID-19 in smokers [21]. Cigarette smoke induces epigenetic modifications of the bronchial epithelium, leading to mucous (goblet) cell metaplasia. As goblet cells are a major source of ACE2 in the lung, this could, in part, justify the increased levels of ACE2 found by Cai and colleagues in lungs of smokers. However, goblet cells are also the main source of mucous, which provides an essential first host barrier to inhaled pathogens that can prevent pathogen invasion and subsequent infection [22,23]. To manage COVID-19 infection, early diagnosis, appropriate treatment, and future control measures are all essential to limit the spread of the virus. Laboratory parameters play an indispensable role in the early assessment of disease etiology, diagnosis, treatment, and follow-up. The SARS-CoV-2 virus might also directly attack the pancreas. All these factors may render infected COVID-19 patients more prone to hyperglycemia [24,25]. Blood glucose level is a routine test that can be carried out in virtually all clinical settings. Among patients with COVID-19, 45.2% had anomalies in blood glucose levels [26]. In agreement with our finding, Wu   *et al.,* [24]. indicated that blood sugar was elevated significantly in Covid-19 patients at admission and this elevation predicted worse outcomes in hospitalized patients with COVID-19. Different recent studies also significant elevation in blood glucose levels in Covid-19 patients [27,28].

The progression of kidney damage is marked by the rise in two important chemical substances in the blood - creatinine and urea whose evaluation in serum helps to assess renal [23]. In agreement with our finding, Cheng *et al.* [29] found that B. urea and S. creatinine were found to be significantly higher in COVID-19 patients compared with survivor cases after cure and the control healthy individuals. LDH is a cytoplasmic glycolytic enzyme used in almost all tissues. Its elevation, in general, indicates tissue damage. Increased LDH was a common finding in Covid-19 infected patients [30].   Our findings supported the effectiveness of TCZ in the prevention or treatment of cytokine storms induced by COVID- 19. In most patients, acute phase reactant levels were decreased and the patients were getting to a stable condition reflected by a later gradual decrease of IL- 6 after TCZ administration. Corticosteroids such as MP are the conventional agents used to fight cytokine storms. However, in the treatment of corticosteroids, a high dose and a long- time period were often required and follow with subsequent risk of side effects. In an attempt to provide a corticosteroid- sparing effect, TCZ was recommended in

COVID- 19 patients to prevent or treat cytokine storms. The rationale for the use of the anti-IL- 6 receptor antibody TCZ in COVID- 19 patients is based on our understanding of the role of IL- 6 in this disease and the experience with this drug in the treatment of cytokine release syndrome caused by chimeric antigen receptors redirect T cells. Some other studies suggested that a single dose of TCZ seems to fail to improve the disease activity in critically ill patients although it was used in combination with glucocorticoid [31,32]. However an other study suggested that repeated doses (even repeated with a lower dose) of TCZ might improve the condition of critically ill patients. Therefore, in addition to the safety advantage, a repeated dose of TCZ is more likely to be effective than glucocorticoid in the treatment of COVID- 19 [33]. Moreover, single dose of TCZ might be expected to benefit these seriously ill patients with about 10 times elevated IL- 6. And the moderately ill patient with an extremely higher level of IL- 6 and d-dimer, almost 90 times of normal, could also benefit from repetitive TCZ therapy. Nevertheless, it seems that repeat the dose at a frequency of daily, every other day, or every 3 days with a totally two to three doses would be sensible in these critically ill patients or patients with an extremely higher level of IL- 6 and other elevated lab parameters [34].

Conclusions

1- The highest mean of Ferritin, D-Dimer, FBS, Blood urea, and LDH recorded among Covid-19 patients before treatment and significantly reduced after IL-6R antagonist treatment
2- Most affected Covid-19 patients were males, smokers and elderly and concluded that these factors seem to be risk for severity

Recommendations

1- Larger studies are needed to confirm our findings
2- Additional studies are required in the role of IL-6R with other disorders and diseases.
3- Furthermore, the treatment duration observed in our study may not be sufficient to make a final conclusion. Therefore, observation with a sufficient number of COVID- 19 patients is still needed to document the effectiveness of TCZ.

References

1. Rizvi MS, Gallo De Moraes A. New decade, old debate: blocking the cytokine pathways in infection-induced cytokine cascade. Crit Care Explor. 2021;3(3):e0364.
2. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5): 105954.
3. Moore J, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473–4.

4. Amer M, Bawazeer M, Dahhan T, Kseibi E, Butt A, Abujazar M, et al. The current use of anti-IL6 and corticosteroids in COVID-19 patients with cytokine-release syndrome. Saudi Crit Care J. 2020;4(5):21–4.

5. Parr JB. Time to reassess tocilizuma's role in COVID-19 pneumonia. JAMA Intern Med. 2021;181(1):12–5.

6. Rubin EJ, Longo DL, Baden LR. Interleukin-6 receptor inhibition in COVID-19—cooling the inflammatory soup. N Engl J Med. 2021;384(16):1564–5.

7. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384(8):693–704.

8. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. 2021;384(16):1491–502.

9. RECOVERY Collaborative Group, Horby PW, Pessoa-Amorim G, et al. Tocilizumab' in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45.

10. COVID-19 real-time learning network. IDSA treatment guideline for COVID-19. 2021.

11. Al-Azzawy, M. A., Qader, S. M., & Mirdan, A. A. (2021). Study of the Relationship between Vitamin D Level and the Increase in the Severity of Covid-19 Infection in Kirkuk City. *Medico-Legal Update*, *21*(2).

12. Tektook, N. K., Yadav, P. R., & Alazzawy, M. A. (2020). Prevalence Corona Virus Disease 2019 (COVID-19) in Baghdad City. *International Journal of Advances in Medical Sciences*, 01-6.

13. Zhang, Z., Li, X., Zhang, W., Shi, Z. L., Zheng, Z., & Wang, T. (2020). Clinical features and treatment of 2019-nCov pneumonia patients in Wuhan: report of a couple cases. *Virologica Sinica*, *35*(3), 330-336.

14. Peruga, A., López, M. J., Martinez, C., & Fernández, E. (2021). Tobacco control policies in the 21st century: achievements and open challenges. *Molecular Oncology*, *15*(3), 744-752.

15. Mizumoto, K., & Chowell, G. (2020). Estimating the risk of 2019 novel coronavirus death during the course of the outbreak in China, 2020. *medRxiv*.

16. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet*, *395*(10229), 1054-1062.

17. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*, *323*(11), 1061-1069.

18. Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., ... & Landry, D. W. (2020). Extrapulmonary manifestations of COVID-19. *Nature medicine*, *26*(7), 1017-1032.

19. Al Hijaj BA, Al-Rubaye AK, Al-Hashim ZT, Mohammed MA, Habib OS. A study on 696 COVID-19 cases in Basrah-southern Iraq: Severity and outcome indicators. Iraqi Natl J Med. 2020;2:27-37.

20. Taher TM. Comorbidity and Risk Factors for COVID-19 Confirmed Patients in Wasit Province, IRAQ. Al-Kindy College Medical Journal. 2020 Jul 24;16(supplement):1-8.

21. Smith JC, Sausville EL, Girish V, Yuan ML, Vasudevan A, John KM, Sheltzer JM. Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. Developmental cell. 2020 Jun 8;53(5):514-29.
22. Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? Intern Emerg Med 2020:1–8.
23. Makoto Miyara FT, Valérie P, Morelot-Panzini C, et al. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. Qeios 2020.
24. Wu, J., Huang, J., Zhu, G., Wang, Q., Lv, Q., Huang, Y., ... & Xiao, H. (2020). Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. *BMJ Open Diabetes Research and Care*, *8*(1), e001476.
25. Stefan, N., Birkenfeld, A. L., & Schulze, M. B. (2021). Global pandemics interconnected—obesity, impaired metabolic health and COVID-19. *Nature Reviews Endocrinology*, *17*(3), 135-149.
26. Cano, E. J., Fuentes, X. F., Campioli, C. C., O'Horo, J. C., Saleh, O. A., Odeyemi, Y., ... & Temesgen, Z. (2021). Impact of corticosteroids in coronavirus disease 2019 outcomes: systematic review and meta-analysis. *Chest*, *159*(3), 1019-1040.
27. Kwan TN, Zwakman-Hessels L, Marhoon N, *et al*. Relative hypoglycemia in diabetic patients with critical illness. *Crit Care Med* 2020;48:e233‑40.
28. Kopp, U. C., & DiBona, G. F. (2020). Neural control of renal function. In *Reflex Control of the Circulation* (pp. 493-528). CRC Press.
29. Cheng, A., Hu, L., Wang, Y., Huang, L., Zhao, L., Zhang, C., ... & Liu, Q. (2020). Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. *International journal of antimicrobial agents*, *56*(3), 106110.
30. Küçükceran, K., Ayrancı, M. K., Girişgin, A. S., Koçak, S., & Dündar, Z. D. (2021). The role of the BUN/albumin ratio in predicting mortality in COVID-19 patients in the emergency department. *The American journal of emergency medicine*, *48*, 33-37.
31. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., ... & Feng, Z. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England journal of medicine*.
32. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of intensive care. 2020 Dec;8(1):1-1.
33. Chiaretti A, Pulitanò S, Barone G, et al. IL-1 beta and IL-6 upregulation in children with H1N1 influenza virus infection. *Mediators Inflamm*. 2013;2013:495848. [PMC free article] [PubMed] [Google Scholar]
34. 8. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood*. 2008;112(10):3959-3964