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A randomized clinical trial study on the efficacy and safety of adalimumab and methylprednisolone pulse therapy in the treatment of COVID-19 patients with acute respiratory distress syndrome

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Abstract

Introduction: Adalimumab reduces the expression of the angiotensin-converting enzyme (ACE2) receptor at the cell surface, therefore it is thought to be effective in treating patients with COVID-19.
Objectives: The present study was conducted to evaluate the effectiveness of adalimumab and pulsed corticosteroids in treating patients with severe acute respiratory failure due to COVID-19.
Patients and Methods: The present double-blind clinical trial study was carried out on patients with COVID-19 referred to Imam Reza hospital, Tehran. Patients were randomly divided into two groups of intervention (patients under standard treatment according to the national protocol of Iran + methylprednisolone + adalimumab) and control (patients under standard treatment according to the national protocol of Iran + methylprednisolone).
Results: The patients' hospitalization information shows that the duration of patients' hospitalization in the intervention group was significantly shorter than their counterparts in the control group ($P=0.041$). Serum levels of total bilirubin on the ninth day ($P=0.043$) and GCS (Glasgow coma scale) on the ninth day ($P=0.041$) and tenth ($P=0.039$) in the adalimumab group were significantly increased compared to the control group. However, the direct bilirubin value on the eighth day (P=0.031), serum creatinine on the 8th ($P=0.047$), 9th ($P=0.047$) and 10th ($P=0.047$) days and also PEEF (pericarditis/pericardial effusion) on the tenth day were significantly lower in the intervention group than the control group.
Conclusion: The administration of adalimumab significantly increases the GCS of COVID-19 patients and reduces the length of hospital stay.
Trial Registration: This study is designed as a double-blind clinical trial (identifier: IRCT20200406046963N2, https://www.irct.ir/trial/55011), and has been approved by the ethics committee in biomedical research of AJA University of Medical Sciences (#IR.AJAUMS.REC.1400.032).

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Introduction

With the outbreak of the novel coronavirus in 2019, the resulting infection has become a global health challenge (1-3). What is observed in most studies is the importance of immune system hyperactivity in the severity of symptoms and processes of multiple organ failure in patients with COVID-19 (4,5). An increase in tumor necrosis factor-alpha (TNF-α) may be associated with severe cases of COVID-19 (4-7). TNF-α inhibitors are effective in preventing lung damage in animal models (8). Therefore, it can be argued that blocking the TNF-α may play a reasonable role in correcting COVID-19. Inflammatory cytokines are mainly secreted by the macrophages. These cytokines are involved in acute phase reactions (4,8). Serum levels of these cytokines are increased in patients with COVID-19 (6,7,9). Overproduction and secretion of TNF-α and other inflammatory factors might suppress the immune system. According to some experimental reports,

Key point

In a double-blind clinical trial study on a group of COVID-19 patients, we found patients who received adalimumab had a significant increase of Glasgow Coma Scale (GCS) and a reduced hospital stay. In our opinion adalimumab is a promising agent in controlling COVID-19 inflammation.

anti-TNF-α therapy improves the disease in mice infected with the flu or respiratory syncytial virus (10,11). Therefore, TNF-α inhibitors may help to improve the inflammatory response in human lung disease (12). It is believed that the administration of a TNF-α inhibitor may reduce the pathological immune response in COVID-19 by reducing inflammatory mediators (13). Various documents have identified corticosteroids as a possible treatment for acute respiratory failure due to COVID-19 (14,15). One of these drugs is also adalimumab, which reduces COVID-19 receptors by decreasing the expression of the angiotensin-converting enzyme (ACE2) receptor on the cell surface (16,17).

Objectives

So far, no specific amount and dose have been introduced in previous studies for adalimumab. Due to few related studies, the guidelines still do not clearly state the effectiveness and safety of the proposed treatment (18-20). Therefore, we intended to evaluate the effectiveness of adalimumab and pulse corticosteroids in treating patients with acute respiratory failure due to COVID-19 in the intensive care unit (ICU).

Patients and Methods

Study design

Patients with the novel coronavirus (COVID-19) referred to Imam Reza hospital in Tehran were included in the study if they had the inclusion and excluded criteria. Inclusion criteria included the COVID-19 patient with moderate to severe severity of hospitalization in the ICU, needing respiratory support, PaO2/FiO2 <300 mm Hg, lactate dehydrogenase (LDH) >450 U/L, progressive course of COVID-19 disease and failure to respond to treatment according to the approved protocol, possibility of intubation 24 hours later. Excluded criteria included uncontrolled diabetes, active bacterial, viral and fungal infections procalcitonin positive and more than 0.5 µg/L or bacterial and fungal culture-positive of each body sample, severe electrolyte disturbance, history of a severe allergy to steroid products, active gastrointestinal bleeding. The research physicians were blinded to the patient group and the patients were blinded to the injected drug (double-blind). A total of 76 patients with COVID-19 were included in the study. Patients were then randomly divided into two groups of intervention (patients under standard treatment according to the national protocol of Iran + methylprednisolone+adalimumab and control (patients under standard treatment according to the national protocol of Iran+ methylprednisolone). All drugs and services provided in this study are provided free of charge to patients, and the costs are covered by the project budget.

In both groups, patients were treated according to Iran's national protocol and received 500 mg of methylprednisolone for three days. In the intervention group, the adalimumab 40 mg (Cinnora brand and Biotechnology Company CinnaGen product) was administered to patients only once on the first day of treatment as a subcutaneous pulse. The variables such as oxygen saturation (SaO2), bilirubin (Bil), lymphocyte, LDH, platelet (Plt), Glasgow Coma Scale (GCS) and spontaneous bacterial peritonitis (SBP) were then measured during the study.

Data analysis

Mean, or median was employed to describe quantitative variables according to the conditions and frequency report was applied for qualitative variables. Independent t test or Mann-Whitney U test was employed to compare quantitative outcomes between the two groups. An independent t-test or Wilcoxon test was used to compare the results before and after the intervention within each group. Statistical analysis were conducted with Statistical Package for the Social Sciences (SPSS), version 16.0 software package. Probability (*P* value) values of less than 0.05 were considered significant.

Results

A total of 94 participants responded to the survey between April 20 and June 20, 2020, with 76 participants with an average age of 66.43 years, providing complete data on the variables in the present analysis (Figure 1). According to Table 1, 36 (47.36%) of all individuals were men and 40 (52.63%) were women. Accordingly, 36 (47.36%) patients had a history of diabetes. However, hypertension with 34 (44.73%) cases and ischemic heart disease (IHD) with 27 (35.52 %) were the following most common underlying diseases; however, there was no significant difference between the two groups.

Table 1 shows that the duration of hospitalization of patients in the intervention group was significantly shorter than their counterparts in the control group ($P=0.041$).

According to the results of Table 2, the passage of time has significantly changed in some indicators. Serum levels of total bilirubin on the ninth day ($P=0.043$) and GCS on the ninth ($P=0.041$) and tenth days ($P=0.039$) in the adalimumab group were significantly increased compared to the control group. However, the direct bilirubin value on the eighth day ($P=0.031$), serum creatinine on the 8th ($P=0.047$), 9th ($P=0.047$) and 10th ($P=0.047$) days and also PEEF (pericarditis/pericardial effusion) on the tenth day were significantly lower in the intervention group than the control group.

Examination of the changes in the studied indices during ten days showed that the numerical value of total bilirubin had the most fluctuation between the two groups, while the serum creatine kinase (CPK) level and the numerical value of urine out in the intervention group increased appropriately compared to the control group (Figure 2).

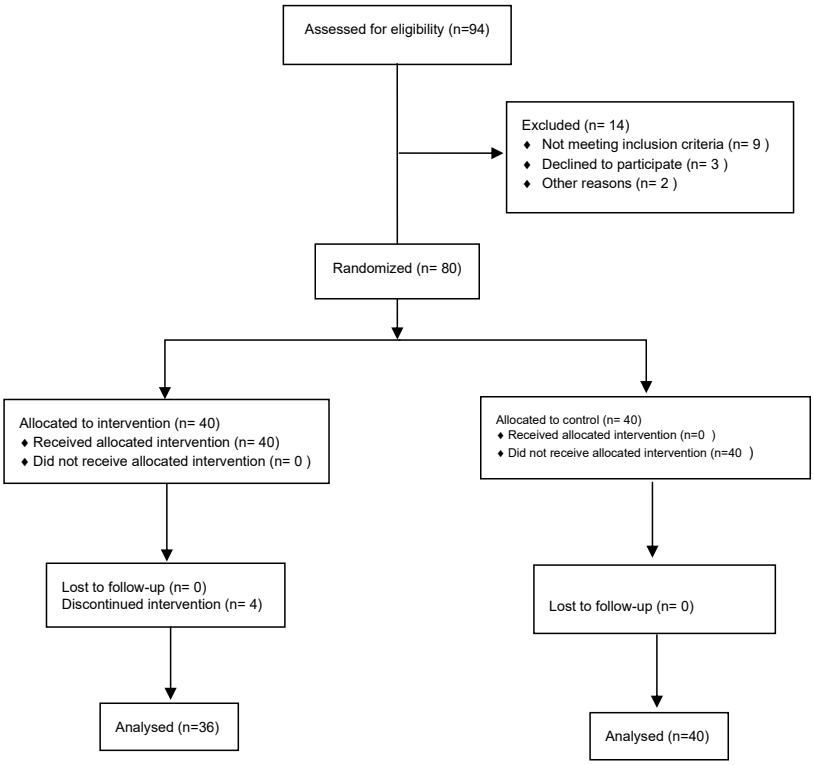

Figure 1. Consort diagram of the study.

Discussion

The immune structure of patients and their cellular immune responses determine the severity of COVID-19 (3). Meanwhile, most patients with a mild form of COVID-19 show a natural immune response to effectively eradicate the virus (5). Therefore, many previous studies have reported that the management of these immune responses can reduce the complications of COVID-19.

As a monoclonal immunoglobulin antibody, adalimumab inhibits TNF-α bioactivity by inhibiting TNF-α interaction with cell surface TNF receptors. This, in turn, inhibits interleukin 6 release, reduction, C-reactive protein, matrix metalloproteinases and adhesion molecules responsible for leukocyte migration (21,22). In this way, it can improve patients with coronavirus by reducing the stressful conditions caused by immune attacks.

The results also showed that the administration of adalimumab in patients with moderate to severe COVID-19 is effective on some clinical and laboratory indicators and leads to significant improvement. What

Table 1. Demographic and hospitalization information of patients in the two groups

Indexes		Intervention group (n=36)	Control group (n=40)	P value
Age (Mean ± SD) (year)		61.40±12.94	71.47±13.07	0.081
Gender	Male (N (%))	16 (44.4%)	20 (50.0%)	0.093
	Female (N (%))	20 (55.5%)	20 (50.0%)	0.998
Diabetes (N (%))		14 (38.8%)	12 (30.0%)	0.107
CVA (N (%))		4 (11.1%)	5 (12.5%)	0.351
Asthma (N (%))		1 (2.7%)	2 (5.0%)	0.073
HTN (N (%)		17 (47.2%)	17 (42.5%)	0.618
HE (N (%)		1 (2.7%)	0 (0.0%)	0.069
AF (N (%))		2 (5.4%)	1 (2.5%)	0.069
IHD (N (%))		12 (33.3%)	15 (37.5%)	0.100
Hypothyroid (N (%))		7 (19.4%)	2 (5.0%)	0.058
Days of mechanical ventilation (Mean ± SD)		6.69 ±5.54	8.19 ±11.23	0.041*
Length in ICU (Mean ± SD)		10.5 ±5.9	9.67 ±9.22	0.098
Length in hospital (Mean ± SD)		12.43±6.4	12.19±10.15	0.074

CVA: cerebrovascular accident, HTN: Hypertension, HE: Hepatic encephalopathy, AF: Atrial fibrillation, IHD: Ischemic heart disease.

Table 2. Evaluation and comparison of clinical and laboratory factors of patients in the intervention group (sample group) compared to the control group

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
SBP (mm Hg)	Intervention	134.6±16.3	133.14±14.9	138.46±19.3	133.0±23.6	133.0±29.4	140.8±14.9	135.8±15.7	132.0±15.9	131.0±19.6	124.5±20.6
	Control	129.7±38.4	128.1±39.6	126.8±38.5	121.7±38.3	123.1±39.6	120.6±45.9	113.0±46.2	110.8±50.9	121.2±37.1	118.5±52.7
	P value	0.176	0.180	0.164	0.103	0.109	0.096	0.082	0.097	0.107	0.194
DBP (mm Hg)	Intervention	79.8±11.3	79.6±8.4	81.6±11.3	80.7±10.5	82.3±10.6	82.0±10.6	77.6±10.9	79.7±11.1	77.2±9.6	73.7±17.4
	Control	71.4±21.5	74.6±22.3	72.2±22.0	72.9±23.4	73.7±24.4	72.3±26.8	66.7±27.2	66.0±30.1	75.8±21.3	77.2±25.1
	P value	0.091	0.102	0.086	0.086	0.087	0.083	0.090	0.061	0.491	0.219
FiO2 (mL)	Intervention	49.5±20.2	51.5±21.9	54.0±24.8	55.9±24.7	55.2±19.0	53.0±18.7	53.8±21.8	58.9±19.4	58.4±18.8	61.8±17.4
	Control	58.7±23.9	62.2±24.2	65.1±25.5	60.48±24.4	63.46±24.9	67.8±23.20	68.00±27.29	65.87±24.9	69.15±28.4	69.9±29.15
	P value	0.094	0.084	0.073	0.084	0.071	0.068	0.061	0.087	0.073	0.08
Plt (10^8/µL)	Intervention	233.8±89.2	209.4±73.2	241.8±118.6	245.5±90.1	236.2±76.1	216.5±73.2	209.6±73.2	209.6±69.6	187.9±67.9	206.1±69.9
	Control	147.2±70.9	216.7±91.05	205.7±84.9	199.8±87.7	184.1±90.9	186.1±101.0	217.8±118.9	200.9±94.5	186.5±63.2	189.64±64.3
	P value	0.064	0.106	0.070	0.066	0.068	0.081	0.148	0.182	0.637	0.107
Bili-D (mg/dL)	Intervention	0.408±0.19	0.380±0.349	0.733±0.408	0.400±0.336	0.742±0.489	0.975±0.906	1.00±0.882	1.10±1.38	0.700±0.141	0.275±0.150
	Control	0.33±0.12	0.32±0.10	0.41±0.25	0.38±0.23	0.56±0.40	0.54±0.30	0.83±1.07	3.00±0.23	0.40±0.18	0.20±0.00
	P value	0.078	0.097	0.061	0.098	0.058	0.051	0.100	0.031*	0.094	0.157
Bili-T (mg/dL)	Intervention	1.233±0.54	1.20±0.604	1.10±0.52	1.14±0.51	1.61±0.48	1.93±1.27	1.72±0.96	1.46±1.93	2.05±0.35	1.10±0.26
	Control	0.92±0.48	1.16±0.56	1.35±0.69	1.45±0.64	1.42±0.49	2.24±2.15	1.18±0.45	1.01±0.54	1.06±0.403	1.00±0.500
	P value	0.087	0.417	0.308	0.291	0.094	0.087	0.182	0.094	0.043*	0.153
GCS	Intervention	14.85±0.60	14.9±0.17	14.7±0.82	14.5±2.13	14.4±1.94	14.4±2.00	14.9±0.426	14.5±1.65	14.5±1.73	14.22±2.33
	Control	12.73±3.02	12.61±3.15	12.02±3.27	12.10±3.34	11.96±3.55	11.47±3.70	11.06±3.88	10.38±4.38	8.65±4.54	8.55±4.26
	P value	0.071	0.068	0.068	0.063	0.061	0.064	0.057	0.053	0.041*	0.0.39*
SrCr (mg/dL)	Intervention	1.21±0.36	1.17±0.36	1.10±0.24	1.06±0.18	1.03±0.27	1.23±1.30	0.99±0.15	0.98±0.204	1.00±0.41	1.11±0.73
	Control	1.59±1.00	1.60±1.14	1.64±1.52	1.57±1.37	1.57±1.18	1.77±1.75	1.78±1.44	2.12±2.24	2.07±2.19	2.10±2.31
	P value	0.063	0.079	0.061	0.059	0.058	0.064	0.054	0.047*	0.047*	0.047*

Table 2. Continued

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Urine-out (mL)	Intervention	1760±863	2140±970	2509±1296	2303±745	2502±770	2501±980	3152±1060	2551±777	3048±1425	2963±1012
	Control	1661.5±808	2005.±1056	2126±1072	2031±1078	2129±1314	1921±1173	1996±1147	1883±912	1620±830	1624±1085
	P value	0.321	0.209	0.210	0.244	0.182	0.103	0.063	0.190	0.100	0.057
O_2-saturation (%)	Intervention	87.71±15.89	86.1±15.6	85..5±15.7	86.5±15.9	86.6±16.3	87.2±16.8	86.1±17.9	86.5±18.9	85.5±21.7	83.8±23.18
	Control	89.39±7.68	89.78±7.22	89.7±7.68	90.4±8.25	89.19±7.10	88.5±9.05	89.19±7.30	88.94±8.04	89.20±4.73	85.50±12.09
	P value	0.110	0.100	0.094	0.098	0.097	0.144	0.098	0.0.95	0.055	0.059
PEEF	Intervention	8.00±0.00	8.66±1.15	7.80±1.78	8.00±1.06	7.00±1.41	7.62±1.50	7.33±1.65	7.10±0.37	6.75±0.49	6.37±0.49
	Control	9.09±3.20	10.91±3.31	11.25±3.19	9.35±3.31	9.90±3.33	10.1±3.92	10.75±2.78	10.50±3.33	11.00±4.41	12.75±5.12
	P value	0.090	0.081	0.079	0.094	0.077	0.082	0.083	0.083	0.054	0.023*
BG (%)	Intervention	182.7±1.67	191.4±11.04	215.1±14.58	214.4±61.15	204.58±55.75	311.3±530.4	259.0±333.2	205.7±90.8	211.8±75.5	192.1±60.69
	Control	189.72±68.2	255.1±296.3	212.0±78.75	206.9±78.15	223.8±88.8	203.3±72.4	188.4±64.1	172.0±55.2	172.7±62.4	167.3±55.0
	P value	0.257	0.099	0.951	0.901	0.764	0.052	0.0.67	0.095	0.081	0.106
CPK (U/L)	Intervention	359.2±385.8	276.5±362.8	241.4±260.7	210.9±153.1	248.9±313.7	240.8±234.7	282.5±331.9	334.8±487.6	404.6±581.1	376.4±301.7
	Control	320.5±717.6	396.3±710.3	513.1±850.7	398.0±560.9	307.6±465.7	278.0±400.7	205.0±237.3	193.5±224.8	238.0±205.8	259.0±205.8
	P value	0.177	0.065	0.048*	0.55	0.110	0.371	0.102	0.080	0.083	0.0134
LDH (U/L)	Intervention	831.1±273.5	943.58±494.9	997.9±429.8	1047±349.8	1082.9±371.6	1177.6±439.3	1139.5±468.5	1064±348.1	1162.1±429.2	1098.4±345.9
	Control	734.6±306.8	952.0±351.4	1072±571.4	1090.8±574	1093.8±953	847.7±389	933.4±131.8	860.2±407.7	901.7±391.9	776.4±409.2
	P value	0.109	0344	0.310	0.739	0.809	0.180	0.200	0.157	0.190	0.100

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Plt: platelets, Bili: Bilirubin, GCS: Glasgow Coma Scale, SrCr: Scavenger Receptor Cysteine-Rich, BG: Blood gas, CPK: Creatine kinase, LDH: Lactate Dehydrogenase, PEEF: Pericarditis/pericardial effusion

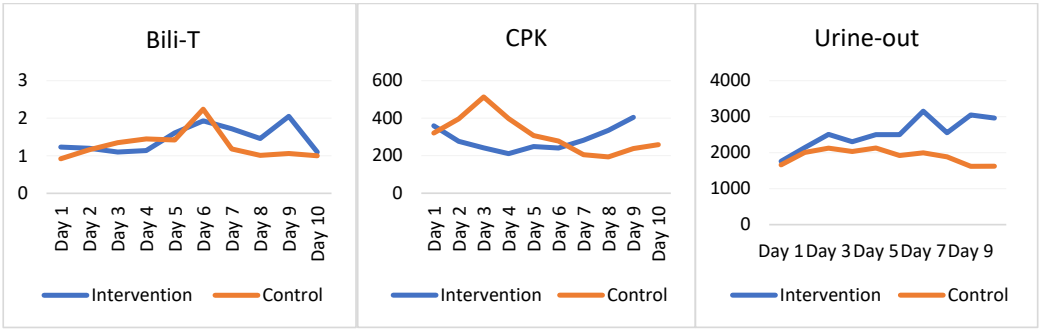

Figure 2. Examining the changes in the studied indicators.

can be clearly described is the effect of taking this drug for more than a week, since all the mentioned indicators showed significant changes after the eighth day. It should be noted that the administration of this drug significantly reduced the length of hospital stay of patients compared to the controls ($P<0.05$). It has previously been shown to be an effective treatment for the management of patients with COVID-19 (23-25). Based on a study, patients with rheumatic disorders who had previously received TNF-α inhibitors developed a mild form of COVID-19 (26). Therefore, it has been suggested that adalimumab, in addition to improving the symptoms of COVID-19, may also be useful in treatment (27).

Conti et al showed that patients with adalimumab-treated psoriasis had no respiratory infection symptoms despite close contact with patients (28). A case of psoriasis was previously reported, which was treated with adalimumab once every two weeks for a year and recovered rapidly from COVID-19. The patient in the authors' ward also quickly recovered (30). In our opinion adalimumab is a promising agent in controlling COVID-19 inflammation.

Conclusion

In this study, administration of adalimumab in patients with COVID 19 admitted to the ICU was associated with a significant increase in GCS patients and a decrease in hospitalization in long-term.

Limitations of the study

One of the limitations of this study was the death of patients during the study, in which case the person was excluded from the study.

Authors' contribution

Conceptualization: RHF, RM, ANA, OY.
Methodology: OY and EH.
Validation: OY and EH.
Formal analysis: RHF, RM, ANA.
Investigation: OY and EH.
Resources: OY and EH.
Data curation: OY, EH, ANA.
Writing–original draft: RHF, RM, ANA, OY.
Writing–review and editing: ANA, EH, OY.
Visualization: OY, EH.
Supervision: OY, EH.
Project administration: EH.

Conflicts of interest

The authors declare there is no conflict of interest.

Ethical issues

The present study was conducted according to the Declaration of Helsinki and with the approval of the ethics committee of AJA University of Medical Sciences. Thus, the Ethics Committee in Biomedical Research of AJA University of Medical Sciences reviewed the implementation process of this study and declared it applicable following its approved protocols (IR.AJAUMS.REC.1400.032). According to the structure defined for the study (randomized clinical trial), informed consent was obtained from all participants before the intervention, and the whole process of treatment and intervention was free in the form of research. The trial protocol was approved by the Iranian Clinical Trial Registry (identifier: IRCT20200406046963N2, https://www.irct.ir/trial/55011). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Hotez PJ. COVID19 meets the antivaccine movement. Microbes Infect. 2020;22:162-164. doi: 10.1016/j.micinf.2020.05.010.
2. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7:11. doi: 10.1186/s40779-020-00240-0.
3. Mitchell SL, George KS. Evaluation of the COVID19 ID NOW EUA assay. J Clin Virol. 2020;128:104429. doi: 10.1016/j.jcv.2020.104429.
4. Robinson DJ, Christenson RH. Creatine kinase and its CK-MB isoenzyme: the conventional marker for the diagnosis of acute myocardial infarction. J Emerg Med. 1999;17:95-104. doi: 10.1016/s0736-4679(98)00129-2.
5. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet. 2020;395:1407-1409. doi: 10.1016/S0140-6736(20)30858-8.
6. Platto S, Xue T, Carafoli E. COVID19: an announced pandemic. Cell Death Dis. 2020;11:799. doi: 10.1038/s41419-020-02995-9.

7. Mair J. Cardiac troponin I and troponin T: are enzymes still relevant as cardiac markers? Clin Chim Acta. 1997;257:99-115. doi: 10.1016/s0009-8981(96)06436-4.
8. Martins JT, Li DJ, Baskin LB, Jialal I, Keffer JH. Comparison of cardiac troponin I and lactate dehydrogenase isoenzymes for the late diagnosis of myocardial injury. Am J Clin Pathol. 1996;106:705-8. doi: 10.1093/ajcp/106.6.705.
9. Kenny G, Mallon PW. COVID19- clinical presentation and therapeutic considerations. Biochem Biophys Res Commun. 2021 Jan 29;538:125-131. doi: 10.1016/j.bbrc.2020.11.021.
10. Ghormade PS, Kumar NB, Tingne CV, Keoliya AN. Distribution & diagnostic efficacy of cardiac markers CK-MB & LDH in pericardial fluid for postmortem diagnosis of ischemic heart disease. J Forensic Leg Med. 2014;28:42-6. doi: 10.1016/j.jflm.2014.09.011.
11. Jaffe AS, Landt Y, Parvin CA, Abendschein DR, Geltman EM, Ladenson JH. Comparative sensitivity of cardiac troponin I and lactate dehydrogenase isoenzymes for diagnosing acute myocardial infarction. Clin Chem. 1996;42:1770-6. doi:10.1093/clinchem/42.11.1770
12. Kabbani N, Olds JL. Does COVID19 Infect the Brain? If So, Smokers Might Be at a Higher Risk. Mol Pharmacol. 2020;97:351-353. doi: 10.1124/molpharm.120.000014.
13. Bertoncelli D, Guidarini M, Della Greca A, Ratti C, Falcinella F, Iovane B, et al. COVID19: potential cardiovascular issues in pediatric patients. Acta Biomed. 2020;91:177-183. doi: 10.23750/abm.v91i2.9655.
14. Vafaie M. State-of-the-art diagnosis of myocardial infarction. Diagnosis (Berl). 2016;3:137-142. doi: 10.1515/dx-2016-0024.
15. Huang HL, Allie R, Gnanasegaran G, Bomanji J. COVID19 -Nuclear Medicine Departments, be prepared! Nucl Med Commun. 2020;41:297-299. doi: 10.1097/MNM.0000000000001183.
16. Zuckier LS, Gordon SR. COVID-19 in the Nuclear Medicine Department, be prepared for ventilation scans as well! Nucl Med Commun. 2020;41:494-495. doi: 10.1097/MNM.0000000000001196.
17. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. 2020;55:105938. doi: 10.1016/j.ijantimicag.2020.105938.
18. Mandel M, Harari G, Gurevich M, Achiron A. Cytokine prediction of mortality in COVID19 patients. Cytokine. 2020;134:155190. doi: 10.1016/j.cyto.2020.155190.
19. Ratliff NB, Estes ML, Myles JL, Shirey EK, McMahon JT. Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. N Engl J Med. 1987;316:191-3. doi: 10.1056/NEJM198701223160405.
20. Thienemann F, Pinto F, Grobbee DE, Boehm M, Bazargani N, Ge J, et al. World Heart Federation Briefing on Prevention: Coronavirus Disease 2019 (COVID-19) in Low-Income Countries. Glob Heart. 2020;15:31. doi: 10.5334/gh.778.
21. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39:2085-2094. doi: 10.1007/s10067-020-05190-5.
22. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497-506. doi: 10.1016/S0140-6736(20)30183-5
23. Gatto M, Bertuzzo E, Mari L, Miccoli S, Carraro L, Casagrandi R, et al. Spread and dynamics of the COVID-19 epidemic in Italy: Effects of emergency containment measures. Proc Natl Acad Sci USA. 2020;117:10484-10491. doi: 10.1073/pnas.2004978117.
24. Bertuzzo E, Mari L, Pasetto D, Miccoli S, Casagrandi R, Gatto M, et al. The geography of COVID-19 spread in Italy and implications for the relaxation of confinement measures. Nat Commun. 2020;11:4264. doi: 10.1038/s41467-020-18050-2.
25. Kuppen PJ, Jonges LE, van de Velde CJ, Vahrmeijer AL, Tollenaar RA, Borel Rinkes IH, et al. Liver and tumour tissue concentrations of TNF-alpha in cancer patients treated with TNF-alpha and melphalan by isolated liver perfusion. Br J Cancer. 1997;75:1497-500. doi: 10.1038/bjc.1997.255.
26. Ferrannini A, Barbieri E, Biggeri M, Di Tommaso MR. Industrial policy for sustainable human development in the post-Covid19 era. World Dev. 2021;137:105215. doi: 10.1016/j.worlddev.2020.105215.
27. Clark J, Vagenas P, Panesar M, Cope AP. What does tumour necrosis factor excess do to the immune system long term? Ann Rheum Dis. 2005;64 Suppl 4:iv70-6. doi: 10.1136/ard.2005.042523.
28. Chathukulam J, Tharamangalam J. The Kerala model in the time of COVID19: Rethinking state, society and democracy. World Dev. 2021;137:105207. doi: 10.1016/j.worlddev.2020.105207.
29. Conti A, Lasagni C, Bigi L, Pellacani G. Evolution of COVID-19 infection in four psoriatic patients treated with biological drugs. J Eur Acad Dermatol Venereol. 2020;34:e360-e361. doi: 10.1111/jdv.16587.
30. Thalha AMM, Lee YY, Besari A, Omar SFS. Have we found the panacea to COVID-19 with remdesivir, an old but newly packaged drug? J R Coll Physicians Edinb. 2020;50:159-161. doi: 10.4997/JRCPE.2020.217.