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Dexamethasone Treatment Considerably Reduces the Levels of Some Inflammatory Cytokines, Lactate Dehydrogenase, and C-Reactive Protein in COVID-19 Pneumonia Patients With Pre-existing COPD

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Abstract

Background: Dexamethasone is the most widely used corticosteroid for treating COVID-19 pulmonary complications. The effects of dexamethasone on serum inflammatory factors, including C-reactive protein (CRP), lactate dehydrogenase (LDH), and cortisol, were evaluated in COVID-19 pneumonia patients with pre-existing chronic obstructive pulmonary disease (COPD) in this study.

Methods: A total of 36 COVID-19 patients with pneumonia who had pre-existing COPD and were critically ill and 56 COVID-19-positive patients without pre-existing COPD were selected. A daily dose of 6–8 mg dexamethasone was administered during the hospitalization period. Some inflammatory markers (TNF-α, IL-10, and IL-6) and the serum levels of cortisol, LDH, and CRP were measured on admission and one week after hospitalization.

Results: TNF-α and IL-6 concentrations were significantly reduced and IL-10 significantly increased in all COVID-19 pneumonia patients with or without pre-existing COPD as a result of a daily dose of dexamethasone. Also, a significant reduction in cortisol, CRP, and LDH was observed following dexamethasone administration in all COVID-19 pneumonia patients, with or without pre-existing COPD, with no correlation with gender, cigarette or waterpipe smoking, or opium abuse.

Conclusion: Our results showed a significant increase in TNF-α, IL-6, IL-10, cortisol, LDH, and CRP and a significant reduction in IL-10 in all critically ill COVID-19 pneumonia patients. Dexamethasone administration significantly reduced cortisol and pro-inflammatory cytokines and also LDH and CRP as the markers of COVID-19 severity.

Keywords: COVID-19, COPD, Dexamethasone, Inflammatory cytokines, Cortisol, C-reactive protein, Lactate dehydrogenase

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Introduction

At the end of 2019, the infectious agent for COVID-19, SARS-CoV-2 or severe acute respiratory syndrome coronavirus 2, appeared in the Chinese city of Wuhan and rapidly spread to most parts of the world (1,2). In most cases, the clinical signs of COVID-19 are mild to moderate, and the patients recover from the infection. However, some patients experience severe clinical symptoms such as pneumonia, respiratory failure, and death (3,4).

COVID-19 infection causes quite a broad range of clinical symptoms among patients, ranging from flu-like syndrome to very severe clinical symptoms such as pneumonia, respiratory failure, and death (5). Extrapulmonary COVID-19 involvement includes smelling sensation fever, cough, rhinorrhea, gastrointestinal signs, such as nausea, vomiting and diarrhea, muscle pain, sore throat, malaise, headache, neurological signs, such as confusion, and hematological abnormalities, including lymphopenia, thrombocytopenia, and elevated D-dimer levels (6-9).

COVID-19 is classified into four stages according to

the disease severity. The first stage of the disease is upper respiratory infection. The main symptoms of the second stage are dyspnea and pneumonia, and the characteristics of the third stage include cytokine storm, the consequent hyperinflammatory state, and the worsening of clinical manifestations. Multiple organ failure and death occur in the 4th stage of COVID-19 infection (10,11).

Based on clinical signs, adult cases of COVID-19 are classified into the four following groups (2, 9):

1. Mild illness: The main clinical symptoms are fever, cough, sore throat, malaise, headache, and muscle pain.
2. Moderate illness: Patients demonstrate peripheral oxygen saturation (SpO2) ≥ 94% and lower respiratory disease signs in images or on clinical examination.
3. Severe illness: Patients present with lung infiltrates > 50% in the chest CT scan, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) < 300 mm Hg, SpO2 < 93% (room air at sea level), or respiratory rates ≥ 30 bpm.
4. Critical illness: This is characterized by septic shock, respiratory failure (requiring mechanical ventilation), multiple organ dysfunctions, and death (2,3,9).

Higher morbidity and mortality have been reported in COVID-19 patients with pre-existing pulmonary disease, depression, severe cardiovascular disease, hepatic failure, immunocompromised patients, uncontrolled diabetes, and severe obesity (12-14), and studies have reported that those with a previous history of chronic obstructive pulmonary disease (COPD) experience more severe COVID-19 and have a higher mortality rate (15). Other investigators have reported that COPD is an independent risk factor that increases COVID-19 severity and mortality rates (15,16).

The immune system plays a vital role in controlling COVID-19. However, unusual immune responses may be associated with abnormal gas exchange in the lungs. Also, the increased serum cortisol in COVID-19 patients has been significantly correlated with a higher mortality rate (17,18). Other investigators have reported that the number of CD4 + T lymphocytes decreases and serum interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels significantly increase. These changes are significantly correlated with COVID-19 severity (19,20). Some investigators have indicated that serum lactate dehydrogenase (LDH) measurement could be a potentially helpful marker for monitoring the response to treatment and assessing the clinical severity in COVID-19 pneumonia (21).

Diagnosis of COVID-19 is confirmed either by a positive test of a nasopharyngeal swab or documented changes in chest CT scan images (11,22,23).

To the best of our knowledge, up to now, no effective pharmaceutical treatment has been developed for COVID-19. The treatment protocol may include supportive care, oxygen therapy in hospitalized patients, and the use of some antiviral drugs such as remdesivir, analgesics, heparin/enoxaparin, dexamethasone, antibiotics, extracorporeal membrane oxygenation (ECMO), and psychotherapy (2,22,24). Also, tocilizumab (Actemra®), an interleukin-6 inhibitor, calms the inflammatory storm, reduces COVID-19-related deaths in severely ill patients, and might be used for COVID-19 pneumonia treatment in hospitalized patients (25,26).

COVID-19 infection has been shown to significantly raise inflammatory markers in patients with COPD history, so corticosteroid therapy should be continued in COPD patients during COVID-19 infection (16,24). Other researchers have indicated that dexamethasone administration (6–8 mg/d) decreases mortality in hospitalized patients with COVID-19 requiring mechanical ventilation (27,28). Dexamethasone administration decreases the COVID-19-induced cytokine storm syndrome; however, it suppresses the immune system, and its use is associated with a decrease in antibody production by B and T lymphocytes and a reduction in the macrophage function, followed by a higher plasma viral load and an increased risk of secondary infections, which necessitates more caution for corticosteroid (dexamethasone) therapy (28,29).

Dexamethasone is used to treat severe COVID-19 cases who need either oxygen therapy or invasive or non-invasive ventilatory support, and, to the best of our knowledge, dexamethasone's effectiveness in COVID-19 pneumonia patients who have pre-existing COPD has not been determined yet. Therefore, this study aimed to examine how effective dexamethasone administration is on the serum levels of cortisol, LDH, C-reactive protein (CRP), and some inflammatory cytokines (TNF-α, IL-6, and IL-10) in hospitalized patients requiring either oxygen therapy or invasive or non-invasive ventilatory support in COVID-19 pneumonia patients with pre-existing COPD.

Methods

Study participants

This study evaluated 36 severely ill COVID-19 pneumonia patients with pre-existing documented COPD (19 men and 17 women aged 41–90 years) admitted to the infectious disease ward or intensive care unit (ICU) of Afzalipour Hospital of Kerman University of Medical Sciences, Kerman, Iran. The patients required either oxygen therapy or invasive or non-invasive ventilatory support. The control group (n = 56, 26 women and 30 men) was chosen from positive COVID-19 pneumonia patients without a pre-existing COPD. The protocol was approved by the Ethics Committee of Kerman University of Medical Sciences approved the protocol (ethics code: IR.KMU.AH.REC.1400.156). COVID-19 pneumonia was confirmed by either a nasopharyngeal swab test or lung involvement compatible with COVID-19

pneumonia (21,22).

The inclusion criteria were respiratory rate > 30 bpm, SpO2 < 93%, lung involvement compatible with COVID-19 pneumonia, and clinical judgment by a pulmonologist or an infectious disease specialist. The exclusion criteria were pre-existing primary adrenal insufficiency or hypoadrenalism and concurrent use of disease-modifying antirheumatic drugs.

A daily dose of 6–8 mg dexamethasone was administered during the hospitalization period. The mean duration of therapy was 5 (3–10) days. Also, the patients received the concurrent World Health Organization (WHO) recommended protocol for COVID-19 drug treatment during the hospitalization period. Written informed consent was obtained from all participants when the participants were conscious or from their guardian or their custodians when the participants were comatose.

Demographic characteristics (age and sex) and length of stay in the hospital were recorded. The patients with or without pre-existing COPD were matched for opium abuse, cigarette and waterpipe smoking, and peripheral capillary oxygen saturation (SpO2) < 93%. All of the patients were tested for serum levels of cortisol and some inflammatory markers (TNF-α, IL-6, and IL-10) on admission and one week after hospitalization. Also, LDH and CRP were measured on admission and one week after hospitalization as the markers of COVID-19 pneumonia severity. Serum levels of IL-6, IL-10, and TNF-α were measured by ELISA method by Karmaniaparsgene Kits (Karmania Pars Gene Co., Kerman, Iran), CRP was detected by turbidimetric reaction, and LDH by enzymatic reaction (oxidation of lactate to pyruvate). The quantitative measurement of serum cortisol was done using the AccuBind ELISA kit (100 N Pointe Dr, Lake Forest, CA 92630, USA).

Statistical analysis

All data have been reported as the mean ± SEM. The student's *t* test was used to compare the continuous variables between the groups. SPSS software version 20 was used for statistical analysis. The criterion for statistical significance was $P < 0.05$.

Results

This study included 92 patients hospitalized with confirmed COVID-19 pneumonia. The subjects included 36 patients with and 56 patients without pre-existing COPD (control group), including 50 males (54.3%) and 42 females (45.6%). The mean ± SD was 71.2 ± 14.1 years for patient age, with non-significant difference between males and females in terms of age. Also, the patients with pre-existing COPD (70.83 ± 15.72 years) and COVID-19 patients without pre-existing COPD were not significantly different in terms of age (71.43 ± 13.22 years) ($P = 0.895$) (Table 1).

Patients with COVID-19 pneumonia with pre-existing COPD had significantly longer mean hospital stays (10.1 ± 6 days) compared to the control group (6 ± 3.5 days) ($P < 0.01$). Cigarette and waterpipe smoking and opium abuse were not significantly different between the two groups.

The SpO2 values between the COVID-19 pneumonia patients with (78.72 ± 11.25%) and without (82.07 ± 10.18%) pre-existing COPD ($P = 0.442$) were not significantly different (Table 1).

Patients with pre-existing COPD (34.8%) recorded significantly higher mortality in hospital than patients without pre-existing COPD (22.6%) ($P < 0.0001$).

The effects of dexamethasone administration on cortisol serum levels

The mean cortisol concentration was not significantly different between the COVID-19 pneumonia patients with and without pre-existing COPD (34.32 ± 8.82 µg / mL and 31.27 ± 8.61 µg /mL, respectively) on admission. We observed significant reduction in serum cortisol levels following daily administration of dexamethasone during the hospitalization period in both COVID-19 pneumonia patients with and without pre-existing COPD (25.61 ± 8.47 µg /mL vs. 14.97 ± 5.53 µg /mL, respectively) ($P < 0.0001$). Also, the results showed that dexamethasone's cortisol-reducing effects were significantly stronger in patients with COPD (25.61 ± 8.47 µg /mL) than in those without pre-existing COPD (14.97 ± 5.53 µg /mL) ($P < 0.0001$). However, this reduction in cortisol level was not significantly correlated with gender, cigarette smoking, waterpipe smoking, or opium abuse (Table 2).

The effects of dexamethasone on TNF-α, IL-6, and IL-10 serum levels

We observed no significant difference in the serum levels of TNF-α (1.24 ± 0.4 pg /mL vs. 1.40 ± 0.49 pg /mL), IL-6 (8.98 ± 3.24 pg /mL vs. 10.76 ± 5.37 pg /mL,), and IL-10 (44.45 ± 3.81 vs. 49.63 ± 4.69 pg /mL) respectively between patients with and without pre-existing COPD ($P < 0.0001$).

Dexamethasone (6-8 mg/d) significantly decreased LDH levels in all COVID-19 pneumonia patients

Table 1. Age, hospitalization duration, and SpO2% of COVID-19 pneumonia patients

Variable	Mean	Standard deviation	*P* value	Median
Age (years)				
COVID-19	71.4	13.2	0.895	73.0
Pre-existing COPD	70.8	15.7		71.5
Hospitalization (days)				
COVID-19	6	3.5	< 0.01	8.5
Pre-existing COPD	10.1	6		13.5
SpO2%				
COVID-19	82.1	10.1	0.442	82.5
Pre-existing COPD	78.7	11.2		84.0

Table 2. The effects of dexamethasone (6-8 mg/d-) during the hospitalization period on IL-6 (pg /mL), IL-10 (pg /mL), TNFα (pg /mL), and cortisol (μg /mL) on hospitalization days and after dexamethasone treatment in critically ill COVID 19 pneumonia patients with and without pre-existing COPD

Variable	COVID-19		COVID-19 + COPD	
	Hospitalization days	Dexamethasone treatment	Hospitalization days	Dexamethasone treatment
Cortisol (μg /mL)	31.27 ± 8.61	14.97 ± 5.53***	34.32 ± 8.82	25.61 ± 8.47**
IL-6 (pg /mL)	10.76 ± 5.37	4.22 ± 3.1***	8.98 ± 3.24	3.43 ± 1.74***
IL-10 (pg /mL)	49.63 ± 4.69	54.36 ± 4.06*	44.45 ± 3.81	53.65 ± 6.54*
TNF-α (pg /mL)	1.40 ± 0.49	0.72 ± 0.32***	1.24 ± 0.40	0.65 ± 0.39***

* $P < 0.001$, ** $P < 0.005$, *** $P < 0.0001$ compared to hospitalization day.

(826.2 ± 238.7 U/L on admission vs. 389.1 ± 142.4 U/L after dexamethasone) ($P < 0.0001$). Also, dexamethasone administration significantly reduced CRP levels in all critically ill COVID-19 pneumonia patients (389.1 ± 140.1 mg/L on admission vs. 125.2 ± 42.4 mg/L after dexamethasone) ($P < 0.0001$) (Table 2).

A daily administration of 6–8 mg dexamethasone during the hospitalization period was associated with a significant rise in serum IL-6 ($P < 0.001$) and IL-10 ($P < 0.0001$) levels and a significant decrease in serum TNF-α levels ($P < 0.0001$) in the group with pre-existing COPD compared to the admission day. The effects of dexamethasone on IL-10, IL-6, and TNF-α serum levels had no correlation with gender, cigarette smoking, water pipe smoking, or peripheral capillary oxygen saturation (SpO2) (Table 2).

The effects of dexamethasone administration on the serum levels of CRP and LDH

Eighty-four (91.3%) of the hospitalized patients had an elevated LDH (> 333 U/L) on admission, and eight patients (8.7%) had LDH levels within the normal range (105–333 U/L).

Dexamethasone (6-8 mg/d) significantly decreased LDH levels in all COVID-19 pneumonia patients (826.2 ± 238.7 U/L on admission vs. 389.1 ± 142.4 U/L after dexamethasone) ($P < 0.0001$). Also, dexamethasone administration significantly decreased CRP levels in all critically ill COVID-19 pneumonia patients (389.1 ± 140.1 mg/L on admission vs. 125.2 ± 42.4 mg/L after dexamethasone) ($P < 0.0001$).

Discussion

Strong upregulation of cytokine production, mainly through the secretion of multiple cytokines, in critically ill COVID-19 pneumonia has been well documented (30). Also, high cytokine levels have been associated with poor COVID-19 prognoses (31). We observed a significant increase in IL-6 and TNF-α concentrations in all admitted COVID-19 patients independent of pre-existing COPD status. In agreement with our results, previous pneumonia studies proposed that TNF-α, IL-10, and IL-6 measurements in patients hospitalized for COVID-19 are potential predictive markers for pulmonary involvement severity (32,33). Thus, we suggest patients hospitalized with COVID-19 pneumonia be routinely and continuously tested for inflammatory cytokines to identify patients at risk of severe disease. Our results indicated that the mortality rate in critically ill COVID-19 patients with pre-existing COPD was significantly higher than COVID-19 patients without any pre-existing COPD, which is in line with previous reports (34-36). Contrary to our results, Ssentongo et al reported that asthma and COPD comorbidities were not significantly associated with a greater risk of mortality in COVID-19 patients (37).

Daily dexamethasone treatment for one week significantly raised IL-10 concentrations and significantly decreased TNF-α and IL-6 in all COVID-19 patients, indicating the beneficial effect of dexamethasone treatment in COVID-19 pneumonia patients. Inflammatory cytokine storms are associated with increased COVID-19 severity (38).

Recent reports have indicated that low doses of dexamethasone administration in patients with severe COVID-19 disease are associated with a significant reduction in mortality rate and duration of mechanical ventilation. However, it has no beneficial effects in the mild form of COVID-19 disease (39,40). In agreement with our results, in another controlled, open-label trial, the same dose of dexamethasone (6 mg/d, 10 days) brought about a significant reduction in 28-day mortality rate among patients with the severe form of COVID-19 disease who were treated with either oxygen alone or invasive mechanical ventilation, but no beneficial effects in patients who did not need respiratory support (27).

The effects of dexamethasone on inflammatory cytokines (IL-10, IL-6, and TNF-α) were not correlated with gender, cigarette smoking, or waterpipe smoking). Contrary to our results, Mirsoleymani et al reported that severe COVID-19 pneumonia was more prevalent in the male gender, and hookah smoking was a significant risk factor in the spread of COVID-19 in Iran (41).

COVID-19 is associated with a significant increase in the risk of acute respiratory distress syndrome, severe pneumonia, cytokine storm syndrome, shock, and death. Corticosteroid administration, especially dexamethasone through the inhibition of phospholipase A2, significantly decreases inflammatory cytokine release. Therefore,

it shows beneficial effects in ameliorating COVID-19 respiratory signs and decreasing the subsequent mortality rate (42).

The results showed elevated cortisol levels in all COVID-19 pneumonia patients on admission, and dexamethasone caused a significant reduction in cortisol values in both COVID-19 pneumonia patients with and without previous history of COPD. However, the dexamethasone-reducing effects were more remarkable in patients without pre-existing COPD. High cortisol level in critically ill COVID-19 pneumonia patients is considered an independent indicator of poor prognosis (43), and dexamethasone administration in a cohort of critically ill COVID-19 patients resulted in a significant reduction in cortisol and some inflammatory cytokines (44). Also, other investigators indicated cortisol level reduction following dexamethasone treatment (45). Comparable to our results, previous reports have indicated the beneficial effects of corticosteroid therapy in COVID-19 patients requiring mechanical ventilation or respiratory support (38). Our results showed that the cortisol-reducing effects of dexamethasone were significantly stronger in COVID-19 patients without pre-existing COPD, which is an interesting finding. The underlying mechanisms require further study in future research.

Our results showed that most of the patients hospitalized with COVID-19 pneumonia (91.3%) had LDH levels above normal values (>333 U/L) (46). Our results completely confirm previous studies reporting that LDH level could be used as an independent predictive parameter for assessing the severity of COVID-19 (21,33). In line with previous studies, we found dexamethasone administration to significantly reduce LDH levels in all critically ill COVID-19 patients. LDH catalyzes lactate-to-pyruvate conversion and is released during tissue damage; thus, it can be used as a non-specific indicator of cellular death and common injuries (47). Comparable to our results, other investigators have reported that high LDH and CRP levels correlate with the severity and poor prognosis of patients hospitalized for COVID-19 (3,47-49).

This study showed a significant reduction in CRP values following dexamethasone administration in all critically ill COVID-19 pneumonia patients. In line with our findings, Hassan et al concluded that daily intravenous dexamethasone (6 mg/d) was associated with a significant reduction in serum levels of CRP, LDH, and IL-6 in severe COVID-19-infected patients (50). Other investigators have reported a marked reduction in CRP values in critically ill COVID-19 patients after treatment with dexamethasone (6 mg/d, IV, 10 days) (51). Also, recent reports have indicated that high-dose methylprednisolone administration for three days followed by oral prednisone for 14 days brings about a significant decrease in the patient hospitalization period and a significant decrease in LDH and CRP levels in severe pneumonia caused by COVID-19 (52).

Dexamethasone is among the drugs prescribed frequently for both hospitalized patients and outpatients throughout the world. Dexamethasone has an anti-inflammatory function, which causes beneficial effects in symptomatic treatments of various diseases, including allergic reactions, collagen-vascular disorders, arthritis, bursitis, tenosynovitis, dermatological disorders, leukemia, gastrointestinal diseases, organ transplants, pulmonary diseases, renal diseases, and many others (53,54). However, long-term use of dexamethasone is associated with a broad range of severe side effects, including fluid retention, moon face, weight gain, visceral fat deposition, myopathy, muscle wasting, thinning of the skin, sleep disturbance, hyperglycemia and diabetes, osteoporosis, and avascular femur necrosis (55-57). It is recommended that the practitioner consider the advantages and disadvantages of treating hospitalized COVID-19 patients with corticosteroids.

Conclusion

In conclusion, a daily 6–8 mg dose of dexamethasone significantly decreased TNFα and Il-6 and a significantly raised serum anti-inflammatory cytokine levels (IL-10) in all critically ill COVID-19 pneumonia patients. Also, dexamethasone caused a remarkable reduction in serum cortisol, and this effect was more prominent in critically ill COVID-19 patients without pre-existing COPD, which is a novel finding. Furthermore, a significant reduction was observed in serum LDH and CRP levels as indicating markers of COVID-19 disease severity.

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Competing Interests

The authors declared no conflict of interest.

Ethical Approval

The protocol was approved by the Ethics Committee of Kerman University of Medical Sciences (ethics code: IR.KMU.

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References

1. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, von Groote TC, Jayarajah U, Weerasekara I, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. J Clin Med. 2020;9(4):941. doi: 10.3390/jcm9040941.
2. Olwenyi OA, Dyavar SR, Acharya A, Podany AT, Fletcher CV, Ng CL, et al. Immuno-epidemiology and pathophysiology of coronavirus disease 2019 (COVID-19). J Mol Med (Berl). 2020;98(10):1369-83. doi: 10.1007/s00109-020-01961-4.
3. Wu F, Zhou Y, Wang Z, Xie M, Shi Z, Tang Z, et al. Clinical characteristics of COVID-19 infection in chronic obstructive pulmonary disease: a multicenter, retrospective, observational study. J Thorac Dis. 2020;12(5):1811-23. doi: 10.21037/jtd-20-1914.
4. Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, et al. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect. 2021;54(1):12-6. doi: 10.1016/j.jmii.2020.05.001.
5. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr. 2020;174(9):882-9. doi: 10.1001/jamapediatrics.2020.1467.
6. Rahman A, Niloofa R, Jayarajah U, De Mel S, Abeysuriya V, Seneviratne SL. Hematological abnormalities in COVID-19: a narrative review. Am J Trop Med Hyg. 2021;104(4):1188-201. doi: 10.4269/ajtmh.20-1536.
7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032.
8. Wang X, Fang J, Zhu Y, Chen L, Ding F, Zhou R, et al. Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang hospital. Clin Microbiol Infect. 2020;26(8):1063-8. doi: 10.1016/j.cmi.2020.03.032.
9. Tsai PH, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK, et al. Clinical manifestation and disease progression in COVID-19 infection. J Chin Med Assoc. 2021;84(1):3-8. doi: 10.1097/jcma.0000000000000463.
10. Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: an overview. Eur J Pharmacol. 2020;889:173644. doi: 10.1016/j.ejphar.2020.173644.
11. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: an overview. J Chin Med Assoc. 2020;83(3):217-20. doi: 10.1097/jcma.0000000000000270.
12. Liu T, Liang W, Zhong H, He J, Chen Z, He G, et al. Risk factors associated with COVID-19 infection: a retrospective cohort study based on contacts tracing. Emerg Microbes Infect. 2020;9(1):1546-53. doi: 10.1080/22221751.2020.1787799.
13. Mousing CA, Sørensen D. Living with the risk of being infected: COPD patients' experiences during the coronavirus pandemic. J Clin Nurs. 2021;30(11-12):1719-29. doi: 10.1111/jocn.15727.
14. Xiao WW, Xu J, Shi L, Wang YD, Yang HY. Is chronic obstructive pulmonary disease an independent predictor for adverse outcomes in coronavirus disease 2019 patients? Eur Rev Med Pharmacol Sci. 2020;24(21):11421-7. doi: 10.26355/eurrev_202011_23635.
15. Lee SC, Son KJ, Han CH, Park SC, Jung JY. Impact of COPD on COVID-19 prognosis: a nationwide population-based study in South Korea. Sci Rep. 2021;11(1):3735. doi: 10.1038/s41598-021-83226-9.
16. Liao SY, Petrache I, Fingerlin TE, Maier LA. Association of inhaled and systemic corticosteroid use with coronavirus disease 2019 (COVID-19) test positivity in patients with chronic pulmonary diseases. Respir Med. 2021;176:106275. doi: 10.1016/j.rmed.2020.106275.
17. Tan T, Khoo B, Mills EG, Phylactou M, Patel B, Eng PC, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol. 2020;8(8):659-60. doi: 10.1016/s2213-8587(20)30216-3.
18. Pal R, Banerjee M, Bhadada SK. Cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol. 2020;8(10):809. doi: 10.1016/s2213-8587(20)30304-1.
19. Sun HB, Zhang YM, Huang LG, Lai QN, Mo Q, Ye XZ, et al. The changes of the peripheral CD4+lymphocytes and inflammatory cytokines in Patients with COVID-19. PLoS One. 2020;15(9):e0239532. doi: 10.1371/journal.pone.0239532.
20. Rostamian A, Ghazanfari T, Arabkheradmand J, Edalatifard M, Ghaffarpour S, Salehi MR, et al. Interleukin-6 as a potential predictor of COVID-19 disease severity in hospitalized patients and its association with clinical laboratory routine tests. Immunoregulation. 2020;3(1):29-36. doi: 10.32598/immunoregulation.3.1.4.
21. Wu MY, Yao L, Wang Y, Zhu XY, Wang XF, Tang PJ, et al. Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-19) pneumonia. Respir Res. 2020;21(1):171. doi: 10.1186/s12931-020-01427-8.
22. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324(8):782-93. doi: 10.1001/jama.2020.12839.
23. Ahuja S, Panigrahi BK, Dey N, Rajinikanth V, Gandhi TK. Deep transfer learning-based automated detection of COVID-19 from lung CT scan slices. Appl Intell (Dordr). 2021;51(1):571-85. doi: 10.1007/s10489-020-01826-w.
24. Luo X, Liu Y, Ren M, Zhang X, Janne E, Lv M, et al. Consistency of recommendations and methodological quality of guidelines for the diagnosis and treatment of COVID-19. J Evid Based Med. 2021;14(1):40-55. doi: 10.1111/jebm.12419.
25. Alzghari SK, Acuña VS. Supportive treatment with tocilizumab for COVID-19: a systematic review. J Clin Virol. 2020;127:104380. doi: 10.1016/j.jcv.2020.104380.
26. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020;18(1):164. doi: 10.1186/s12967-020-02339-3.
27. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384(8):693-704. doi: 10.1056/NEJMoa2021436.
28. Lim MA, Pranata R. Worrying situation regarding the use of dexamethasone for COVID-19. Ther Adv Respir Dis. 2020;14:1753466620942131. doi: 10.1177/1753466620942131.
29. Li N, Jie Z. The application of corticosteroids in COVID-19: a two-edged sword. J Transl Int Med. 2020;8(2):66-70. doi: 10.2478/jtim-2020-0011.
30. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev. 2020;53:38-42. doi: 10.1016/j.cytogfr.2020.04.002.
31. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol. 2020;11:1708. doi: 10.3389/fimmu.2020.01708.
32. Buszko M, Park JH, Verthelyi D, Sen R, Young HA, Rosenberg

AS. The dynamic changes in cytokine responses in COVID-19: a snapshot of the current state of knowledge. Nat Immunol. 2020;21(10):1146-51. doi: 10.1038/s41590-020-0779-1.
33. Zeng Z, Yu H, Chen H, Qi W, Chen L, Chen G, et al. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. Crit Care. 2020;24(1):525. doi: 10.1186/s13054-020-03255-0.
34. Rabbani G, Shariful Islam SM, Rahman MA, Amin N, Marzan B, Robin RC, et al. Pre-existing COPD is associated with an increased risk of mortality and severity in COVID-19: a rapid systematic review and meta-analysis. Expert Rev Respir Med. 2021;15(5):705-16. doi: 10.1080/17476348.2021.1866547.
35. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Med Virol. 2020;92(10):1915-21. doi: 10.1002/jmv.25889.
36. Ge E, Li Y, Wu S, Candido E, Wei X. Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: a population-based cohort study. PLoS One. 2021;16(10):e0258154. doi: 10.1371/journal.pone.0258154.
37. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. PLoS One. 2020;15(8):e0238215. doi: 10.1371/journal.pone.0238215.
38. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021;93(1):250-6. doi: 10.1002/jmv.26232.
39. Ahmed MH, Hassan A. Dexamethasone for the treatment of coronavirus disease (COVID-19): a review. SN Compr Clin Med. 2020;2(12):2637-46. doi: 10.1007/s42399-020-00610-8.
40. Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intensive Care Med. 2021;47(5):521-37. doi: 10.1007/s00134-021-06394-2.
41. Mirsoleymani S, Nekooghadam SM, Ahmadi Marzaleh M, Peyravi M, Soltani A, Sharififar S, et al. Assessment of risk factors for severe coronavirus disease 2019 among Iranian patients. Iran Red Crescent Med J. 2020;22(2):e72. doi: 10.32592/ircmj.2020.22.9.72.
42. Noreen S, Maqbool I, Madni A. Dexamethasone: therapeutic potential, risks, and future projection during COVID-19 pandemic. Eur J Pharmacol. 2021;894:173854. doi: 10.1016/j.ejphar.2021.173854.
43. Świątkowska-Stodulska R, Berlińska A, Puchalska-Reglińska E. Cortisol as an independent predictor of unfavorable outcomes in hospitalized COVID-19 patients. Biomedicines. 2022;10(7):1527. doi: 10.3390/biomedicines10071527.
44. Asif S, Frithiof R, Larsson A, Franzén S, Anderberg SB, Kristensen B, et al. Immuno-modulatory effects of dexamethasone in severe COVID-19-a Swedish cohort study. Biomedicines. 2023;11(1):164. doi: 10.3390/biomedicines11010164.
45. Kino T, Burd I, Segars JH. Dexamethasone for severe COVID-19: how does it work at cellular and molecular levels? Int J Mol Sci. 2021;22(13):6764. doi: 10.3390/ijms22136764.
46. Buckner SL, Loenneke JP, Loprinzi PD. Cross-sectional association between normal-range lactate dehydrogenase, physical activity and cardiovascular disease risk score. Sports Med. 2016;46(4):467-72. doi: 10.1007/s40279-015-0457-x.
47. Zhang YQ, Dai HB, Wang JH, Li XY, Dai SM, Yao DD, et al. [Prognostic significance of serial determinations of lactate dehydrogenase in follow-up for patients with myelodysplastic syndrome]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2011;19(1):85-9. [Chinese].
48. Ali AH, Mohamed SO, Elkhidir IH, Elbathani ME, Ibrahim AA, Elhassan AB, et al. The association of lymphocyte count, CRP, D-dimer, and LDH with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Sudan J Med Sci. 2020;15(2):9-23. doi: 10.18502/sjms.v15i5.7146.
49. Choi YJ, Song JY, Hyun H, Nham E, Yoon JG, Seong H, et al. Prognostic factors of 30-day mortality in patients with COVID-19 pneumonia under standard remdesivir and dexamethasone treatment. Medicine (Baltimore). 2022;101(38):e30474. doi: 10.1097/md.0000000000030474.
50. Hassan ME, Hasan HM, Sridharan K, Elkady A, ElSeirafi MM. Dexamethasone in severe COVID-19 infection: a case series. Respir Med Case Rep. 2020;31:101205. doi: 10.1016/j.rmcr.2020.101205.
51. Kooistra EJ, van Berkel M, van Kempen NF, van Latum CRM, Bruse N, Frenzel T, et al. Dexamethasone and tocilizumab treatment considerably reduces the value of C-reactive protein and procalcitonin to detect secondary bacterial infections in COVID-19 patients. Crit Care. 2021;25(1):281. doi: 10.1186/s13054-021-03717-z.
52. Pinzón MA, Ortiz S, Holguín H, Betancur JF, Cardona Arango D, Laniado H, et al. Dexamethasone vs methylprednisolone high dose for COVID-19 pneumonia. PLoS One. 2021;16(5):e0252057. doi: 10.1371/journal.pone.0252057.
53. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30. doi: 10.1186/1710-1492-9-30.
54. Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. Otolaryngol Clin North Am. 2010;43(4):753-68. doi: 10.1016/j.otc.2010.04.003.
55. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. Expert Opin Drug Saf. 2016;15(4):457-65. doi: 10.1517/14740338.2016.1140743.
56. Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-term systemic corticosteroid exposure: a systematic literature review. Clin Ther. 2017;39(11):2216-29. doi: 10.1016/j.clinthera.2017.09.011.
57. Langarizadeh MA, Ranjbar Tavakoli M, Abiri A, Ghasempour A, Rezaei M, Ameri A. A review on function and side effects of systemic corticosteroids used in high-grade COVID-19 to prevent cytokine storms. EXCLI J. 2021;20:339-65. doi: 10.17179/excli2020-3196.