Serum cortisol concentration and COVID-19 severity: a systematic review and meta-analysis

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ABSTRACT

The novel COVID-19 outbreak is a major health threat to human beings with multiorgan injuries. However, its endocrine system manifestations are much less studied. In this study, we aimed to reassess the available findings on the association between cortisol level and severity of COVID-19 infection. We conducted a systematic search on Medline/PubMed, Scopus, Web of Science, and Cochrane Library databases. To pool data, a random-effects model was performed depending on the heterogeneity among studies. Sensitivity analysis was also carried out by removing each study systematically. In addition, subgroup and meta-regression analyses were performed depending on the presence of the variables of sex and age. Subsequently, 11 studies (5 observational studies and 6 case reports) were included in the meta-analysis. Pooled analysis on the observational studies showed significantly higher levels of cortisol in patients with severe COVID-19 in comparison with those with mild-to-moderate COVID-19 (standardized mean difference: 1.48 µg/dL; 95% CI (0.51 to 2.46); p=0.003). Assessment of the results of case reports revealed that the patients with severe COVID-19 demonstrated higher cortisol levels than the patients with mild-to-moderate COVID-19. No publication bias was observed using the Begg's (p=0.08) and Egger's tests (p=0.09). Meta-regression illustrated a significant correlation between cortisol levels with sex. The serum cortisol level seems to be higher in patients with severe COVID-19 infection. This finding could be helpful to detect patients with poor prognosis at early stages of the disease, although age and sex may modify this level.

Significance of this study

What is already known about this subject?
► Due to COVID-19 pandemic, compounds are needed to separate severe status of COVID-19 form the mild-to-moderate ones.
► Several studies have reported serum cortisol level in severe COVID-19 in comparison with mild-to-moderate COVID-19.
► The results concerning the association between serum cortisol level and severity of COVID-19 are conflicting and inclusive.

What are the new findings?
► Serum cortisol level significantly increased in patients with severe COVID-19 compared with those with mild-to-moderate COVID-19.
► The results of the subgroup analysis showed higher levels of cortisol in men than in women in the severe form of COVID-19.

How might these results change the focus of research or clinical practice?
► Significant increase in serum cortisol level in patients with severe COVID-19 could be an effective biomarker for detection of serious complications in those hospitalized in the intensive care unit. Therefore, these data may be useful for clinicians.

INTRODUCTION

A novel coronavirus (COVID-19), caused by SARS-CoV-2, has infected about 152,000,000 persons and caused more than 3 million deaths (May 01, 2021) worldwide since its sudden epidemic in Wuhan, China in December 2019.[1][2] Physiological stress from serious disease and elective surgery elevates cortisol concentrations and bioavailability in serum through the activation of the hypothalamic–pituitary–adrenal (HPA) axis, reduced cortisol synthesis, and the binding protein level like cortisol-binding globulin.[3][4] Cortisol elevation is a necessary component of the body's stress response, causing adaptive improvements in metabolism, immune regulation, and cardiovascular

function.[3] Adrenal insufficiency is a problem in which the adrenal glands do not release enough cortisol, and it is usually known by a cortisol reaction to corticotrophin of lower than 21 μg/dL.[5] Cortisol levels rise in direct proportion to the severity of sepsis. Certainly, glucocorticoids elevate the recruitment of the inflammatory agent and determine the systemic inflammatory response.[6] However, in about 30%–70% of sepsis cases, the adrenal reaction is insufficient or there is glucocorticoid periphery resistance, all of which are linked to a weak prognosis and necessary supplementation.[7]

Meanwhile, immunomodulatory effects are found in endocrine hormones. The path and effects of HPA axis activation are influenced by endocrine dysfunction. Cortisol and

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dehydroepiandrosterone (DHEA), two adrenal gland hormones, have opposite impacts on immune activity.[8 9] DHEA, a precursor to estrogens and androgens, and sulfated form of DHEA are the most abundant adrenal steroids controlling the synthesis and activity of cortisol, the stress hormone. Adrenal hormones formed in response to infection will control immune function on their own.[10] Glucocorticoids have a significant anti-inflammatory activity by interacting with glucocorticoid receptors in the cytoplasm of immune cells. Infection causes cytokine-producing immune cells to become more responsive to glucocorticoids.[8]

The effects of COVID-19 on cortisol are still uncertain. It has been recommended that SARS-CoV, the precursor of SARS-CoV-2, could activate an immunogenic reaction to adrenocorticotropic hormones.[11] SARS-CoV-2 could employ similar pathways to increase morbidity and mortality by causing a cortisol synthesis insufficiency linked to a serious disease.[11 12] The key glucocorticoid cortisol can cross the blood–brain barrier and affect central nervous system activity by stimulating central corticosteroid receptors.[13 14] Since stress is also linked to mood shifts, researchers have looked into the effects of cortisol on emotional processes in a variety of studies. Stress has been revealed to have a substantial impact on negative affect, while cortisol levels and negative affective state have been shown to be related.[15]

To date, several inflammatory prognostic markers for this disease have been introduced, such as interleukin-6 (IL-6), C reactive protein (CRP), and several others, but no specific marker has yet been identified in association with endocrine hormone levels, such as cortisol, for the prognosis of the disease outcome.[16] However, there is an immediate need to identify better and specific markers in this regard. In addition, we are informed that no meta-analysis studies have been published in this area. The purpose of the current meta-analysis was to review the available studies on the role of cortisol in patients with COVID-19 entirely to improve survival rates and decrease infection and fatality in this pandemic.

MATERIALS AND METHODS
Study protocol
The current study has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17]

Eligibility criteria
In order to investigate the association between cortisol level and COVID-19 infection severity in patients with confirmed SARS-CoV-2 infection, we included all published articles assessing the serum level of cortisol and severe outcome of COVID-19 infection without any language limitations. In addition, study articles were classified into two groups based on study design, including observational and case report studies. We further excluded review articles, letters, books and also studies with incomplete data from our meta-analysis. We also noted that none of the included studies in this meta-analysis reported a known underlying adrenal disease and corticosteroid use before admission to the hospital due to previous underlying disease, so we performed this meta-analysis by assuming that none of the patients had such diseases.

Search strategies
We performed a literature search using the online databases of Medline/PubMed, Web of Science, Scopus and Cochrane Library for relevant publications up to April 2021. However, we used the following medical subject headings term in our search strategy: ("COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "new coronavirus" OR "2019-nCoV") AND ("Cortisol" OR "Cortisol Level" OR "Serum Cortisol Level" OR "Cortisol Concentration" OR "Adrenal"). In addition, we searched all reference lists of retrieved articles to get missed studies. The duplicated articles were removed from the analysis. The systematic search and reviewing of the full-text articles was performed by two independent reviewers (NA-D and MK).

Data extraction process and assessment for study quality
Data that include authors' names, date of study, country, study design, sample size, serum level of cortisol and outcome of the studies were extracted by two independent investigators, as appropriate. The Newcastle–Ottawa Scale (NOS) was used for quality assessment of the observational studies.[18] Based on the NOS system, a maximum of 9 points can be awarded to each article. The selection, comparability, and exposure of every included study were evaluated and assigned a score from 0 to 9. In this study, the NOS scores <4, 4–6, and ≥7 were considered as low-quality, moderate-quality and high-quality studies, respectively. Furthermore, 7 case report studies were systematically assessed for risk of bias using instructions presented in the Joanna Briggs Institute (JBI) critical appraisal checklist.[19] The following questions were used for the evaluation of every case report study: (1) Were the patient's demographic characteristics clearly described?; (2) Was the patient's history clearly described and presented as a timeline?; (3) Was the current clinical condition of the patient on presentation clearly described?; (4) Were diagnostic tests or assessment methods and the results clearly described?; (5) Was the intervention(s) or treatment procedure(s) clearly described?; (6) Was the post-intervention clinical condition clearly described?; (7) Were adverse events (harms) or unanticipated events identified and described?; (8) Does the case report provide takeaway lessons? According to the JBI checklist, a judgment of 'yes' showed high quality, whereas 'no' indicated low quality, labeling a question as 'unclear' or 'not applicable' indicated an unclear or unknown risk of bias.

Statistical analysis
A random-effects model was used to calculate the pooled effect size. The standardized mean difference (SMD) with 95% CI was used for data analysis in observational studies. Moreover, we also analyzed significance and calculated CI for SMD effect size using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method regarding the small number of studies and between-study heterogeneity. Evaluating the results of case report studies was performed using reported characteristics of patients with severe COVID-19 and high cortisol level in comparison with patients with mild-to-moderate COVID-19. In cases where the circulating levels of cortisol were reported using median and IQR values, mean value was estimated using a method previously defined.[20] To find the heterogeneity among included studies, the heterogeneity was measured using the Higgins I^2 (p<0.1, I^2 >50% was considered
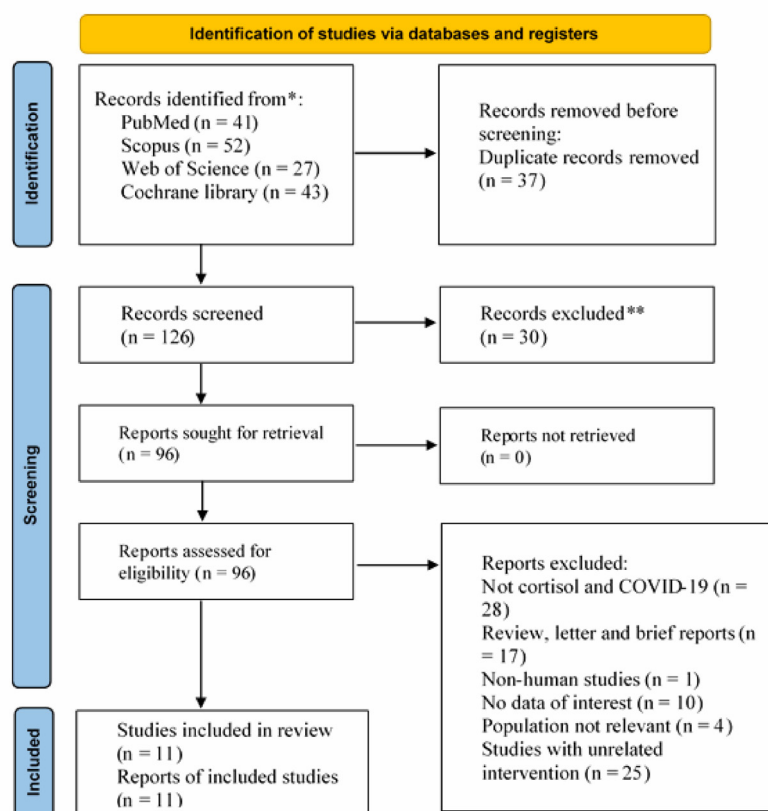
Figure 1 Process of study selection based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

representative of significant statistical heterogeneity).[21] To explore the source of significant heterogeneity between the studies, subgroup analysis was performed according to a subgroup of sex (male and female). The potential publication bias in observational studies was evaluated through a visual inspection of funnel plot and the Begg's and Egger's tests. The trim-and-fill analysis was used to adjust any significant publication bias detected. In addition, a sensitivity analysis was performed to assess the effect of each study on the overall effect size by using the 'leave-one-out' method by removing the step-by-step study in the analysis. Subsequently, a random-effects meta-regression analysis was performed on the observational studies, using an unrestricted maximum likelihood method, to determine the association between the circulating levels of cortisol with age and sex (male and female). A p<0.05 was considered statistically significant. Comprehensive Meta-Analysis V.2 software was used for the data analysis (Biostat, New Jersey, USA).

RESULTS
Study selection and characteristics
A total of 163 records was identified from four main databases: PubMed, Scopus, Web of Science and Cochrane Library up to April 2021. After the exclusion of duplicates and irrelevant studies, 11 articles were included in this systematic review and meta-analysis. A PRISMA flow chart detailing the process of study selection is shown in figure 1.

The primary information of included studies
The summary characteristics of all included studies are presented in table 1. Of these 11 studies, 4 and 3 studies were performed in the UK and Iran, respectively. The other studies were from Brazil, Cameroon, UAE and Israel. All studies were published during 2020 and 2021. Seven studies were designed as case reports and 4 as observational studies (cohort and cross-sectional). The 476 patients with COVID-19 infection participated in this meta-analysis. Of the participants, 374 (78%) were male and 102 (22%) were female. The NOS scores ranged from 4 to 9. Quality assessment of case report studies indicated that most of the case report studies did not provide sufficient data about question 8, while other questions from the JBI checklist were sufficiently addressed by most of the case report studies. Details of quality assessment of case report studies are summarized in table 2.

The relationship of high cortisol levels with severity of COVID-19 based on observational studies
The meta-analysis of observational studies demonstrated significantly higher levels of cortisol in patients with severe COVID-19 in comparison with mild-to-moderate COVID-19 controls (SMD: 1.48 µg/dL; 95% CI (0.51 to 2.46); p=0.003) (figure 2). Calculation of HKSJ adjustment was also significant (SMD: 1.49 µg/dL; 95% CI (0.48 to 2.55); p=0.007) regarding the small number of included studies. There was a significant heterogeneity among included studies (I^2=90.4%, p<0.001). To find sources

Table 1 The study characteristics included in this meta-analysis

Author	Country	Ratio of sex (M/F)	Study design	Sample size Non-severe	Sample size Severe	Cortisol (µg/dL) Non-severe	Cortisol (µg/dL) Severe	Outcome	NOS score
Frankel et al[26]	Israel	F	Case report	1	–	<1	–	COVID-19 infection is associated with BAH. Adrenal insufficiency is life-threatening, therefore we suggest considering performing early adrenal axis testing for patients with COVID-19 with clinical suspicion of adrenal insufficiency.	–
Elkhouly et al[27]	UK	M	Case report	–	1	–	26.6	This study reported that adrenal hemorrhage should be considered as a rare complication of COVID-19 and potentially lethal.	–
Etoga et al[7]	Cameroon	45/35	Cross-sectional	70	10	4.5±0.5	11.45±1.8	This study recorded higher levels of cortisol among COVID-19 cases that need further oxygen therapy than those with mild condition.	8
Hashim et al[28]	UAE	M	Case report	1	–	4.6	–	SARS-CoV-2 can knock down the host's cortisol stress response and clinicians must be vigilant about the possibility of an underlying relative cortisol deficiency in patients with COVID-19.	–
Heidarpour et al[29]	Iran	M	Case report	1	–	12	–	This study suggested that early detection of adrenal insufficiency among critically ill patients infected with SARS-CoV-2 could be lifesaving.	–
Vaez Mahdavi et al[10]	Iran	56/5	Cohort	46	15	21.4±11.2	26.2±13.7	The current study results support that COVID-19 affects the patients' body via mechanisms related to the effects of DHEA-S and cortisol.	9
Ramezani et al[24]	Iran	17/13	Cross-sectional	26	4	26.2±6.5	36.1±3.2	This study significantly correlated higher levels of cortisol in non-survived patients of COVID-19 in comparison with surviving patients.	8
Freire Santana et al[6]	Brazil	M	Case series	16	12	22.4	48.01±21.2	In this study, adrenal lesions are frequent in patients with severe COVID-19. No cortisol level less than 10 µg/dL, which is a reliable and widely available laboratorial marker of adrenal insufficiency in critically ill patients, could contribute to the lethal outcome.	–
Sharrack et al[30]	UK	M	Case report	1	–	31.3±2.7	–	AH and high serum cortisol are rare complications of COVID-19 infection.	–
Tan et al[11]	UK	240/51	Cohort	132	159	22.4±10	18.8±8.1	This study revealed the association between high serum total cortisol concentrations and mortality from COVID-19.	9
Kumar et al[31]	UK	F	Case report	1	–	21.7	–	COVID-19 creates a hypercoagulable state, with acute adrenal infraction as a possible prothrombotic complication.	–

AH, adrenal hemorrhage; BAH, bilateral adrenal hemorrhage; DHEA-S, dehydroepiandrosterone-sulfated form; F, female; M, male; NOS, Newcastle–Ottawa Scale.

Table 2 Quality assessment of case report studies involved in the meta-analysis

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Frankel et al[26]	Y	N	Y	Y	N	Y	U	Y
Elkhouly et al[27]	Y	N	N	Y	N	Y	U	Y
Hashim et al[28]	Y	Y	Y	Y	Y	Y	U	Y
Heidarpour et al[29]	Y	Y	Y	Y	U	Y	U	Y
Freire Santana et al[6]	Y	Y	N	N	U	U	N	Y
Sharrack et al[30]	Y	N	Y	Y	Y	Y	Y	Y
Kumar et al[31]	Y	N	Y	Y	Y	Y	Y	Y

Q1: Were the patient's demographic characteristics clearly described?
Q2: Was the patient's history clearly described and presented as a timeline?
Q3: Was the current clinical condition of the patient on presentation clearly described?
Q4: Were diagnostic tests or assessment methods and the results clearly described?
Q5: Was the intervention(s) or treatment procedure(s) clearly described?
Q6: Was the post-intervention clinical condition clearly described?
Q7: Were adverse events (harms) or unanticipated events identified and described?
Q8: Does the case report provide takeaway lessons?
N, no; Q, question; U, unclear; Y, yes.

of significant heterogeneity, subgroup and meta-regression analyses were performed.

The relationship of high cortisol levels with severity of COVID-19 based on case reports

We evaluated the relationship between higher cortisol levels and the severity of COVID-19 among case report studies that were reported in the mentioned electronic databases. Evaluation of the circulating cortisol level among case report studies showed that patients with severe COVID-19 have higher levels of cortisol than those with non-severe COVID-19.

Publication bias

To assess publication bias of observational studies, the Begg's rank correlation (Kendall's tau with continuity correction=0.7, Z=1.71, two-tailed p=0.08) and Egger's linear regression tests (intercept=3.9, SE=1.6; 95% CI=−1.1 to 9.1, t=2.4, df=3, two-tailed p=0.09) were indicated absence of publication bias. The funnel plot of the study precision (inverse SE) by effect size (SMD) was symmetric and suggested no potential publication bias in reporting the circulating levels of cortisol in patients with COVID-19 (figure 3). The observed publication bias was imputed using trim-and-fill correction. There were two imputed studies.

Sensitivity analysis

Sensitivity analysis was performed on the observational studies using the 'leave-one-out' method. Sensitivity analysis showed that the pooled effect size was not altered when every single study was in turn removed (effect size ranged between 0.74 and 1.87 µg/dL). Circulating cortisol level remained significantly higher (SMD: 1.91 µg/dL; 95% CI (0.77 to 1.61); p<0.001) in patients with severe COVID-19 after excluding the study with larger sample size (figure 4).
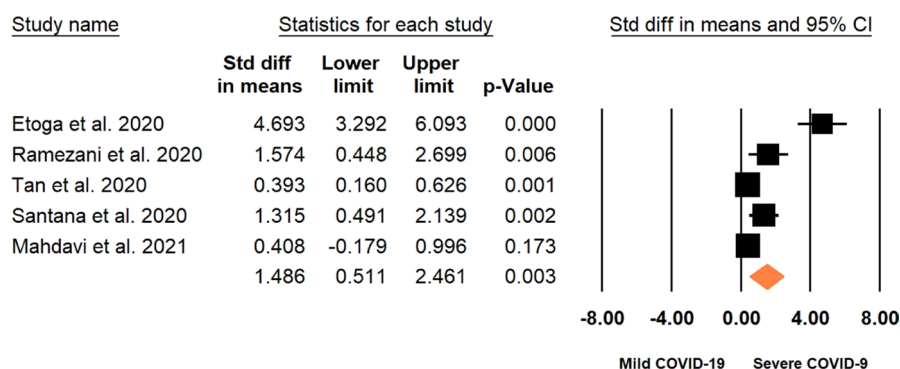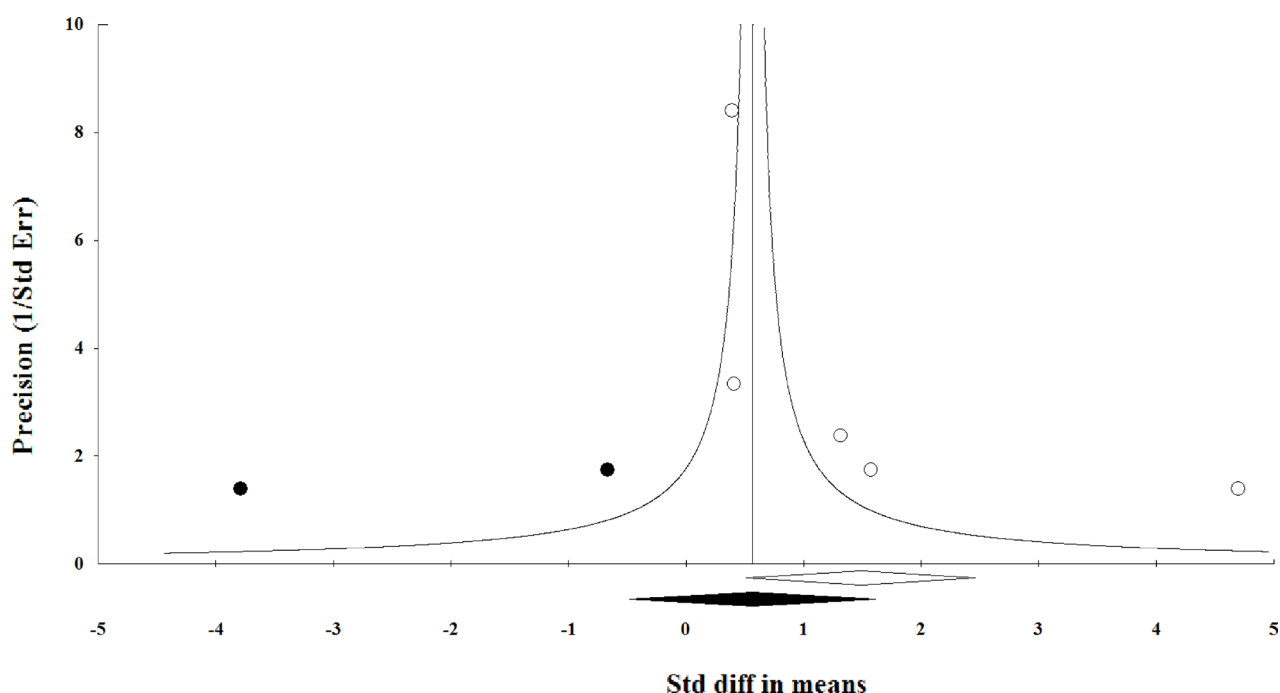
Figure 2 Forest plot evaluating standardized mean differences and 95% CIs for the relationship between the circulating cortisol level and COVID-19 severity. Data were analyzed using a random-effects model.

Subgroup analysis and meta-regression analysis

To explore significant heterogeneity among studies, subgroup analysis was performed. Analysis of the subgroup of sex (male, female) showed that the circulating cortisol levels were not significant in male patients with severe COVID-19 (SMD: 0.5 µg/dL; 95% CI (−0.21 to 1.23); p=0·17) compared with female patients with severe COVID-19 (figure 5). Besides, to get more source of heterogeneity, random-effects meta-regression was performed on the observational studies. Meta-regression indicated no significant association between circulating cortisol level and age (slope: −0.14; 95% CI (−0.20 to −0.08); p<0.001). However, there was a significant positive association with male sex (slope: −0.016; 95% CI (−0.026 to −0.006); p<0.001) and female sex (slope: −0.012; 95% CI (−0.020 to −0.004); p=0.001) (online supplemental figure 1). Therefore, the age and sex variables show partly significant heterogeneity among included studies.

DISCUSSION

The novel emerging coronavirus (SARS-CoV-2) has threatened people all over world. The disease has a broad range of clinical manifestations, from asymptomatic to fatal infection. Additionally, there is no definitive cure for the disease and only supportive therapies are available.[22] Recent studies have reported that the cytokine storm (hyperinflammation) is one of the main mechanisms of acute respiratory distress syndrome and multiple organ dysfunction syndromes in patients with COVID-19 .[23] However, there is limited information on the relationship between COVID-19 and endocrine status. It can be said that stress during the disease leads to the HPA axis activation and as a result elevates the level of serum cortisol in patients.[24] Hence, to deal with the new emerging COVID-19 infection with such a wide range of complications, there is an urgent need to identify and introduce factors associated with the prediction of disease outcome.

Figure 3 Funnel plot of publication bias detailing the study precision (inverse SE) by effect size (standard difference in means) for the relationship between the circulating cortisol level and COVID-19 severity. Data were analyzed using a random-effects model.
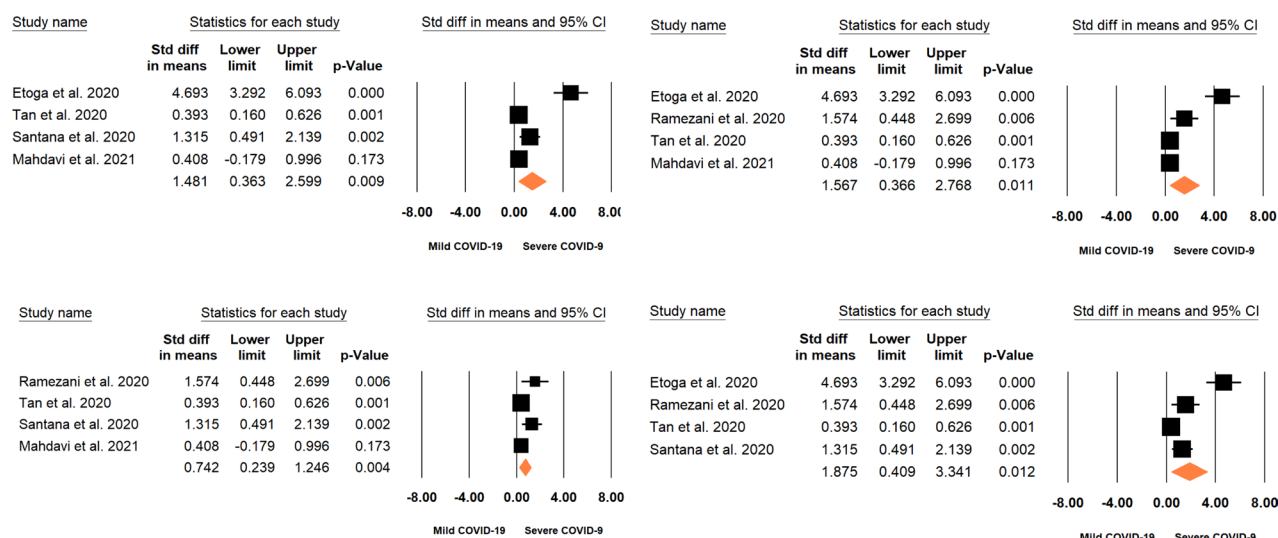
Figure 4 Sensitivity analyses were performed using 'leave-one-out' method. The pooled effect size was estimated when every single study was in turn removed. Data were analyzed using a random-effects model.

In this meta-analysis, we aimed to analyze all the available data regarding serum cortisol level and disease severity in patients with COVID-19 for the first time. This work was based on 496 patients from 11 studies assessing the cortisol level in patients with severe versus non-severe evidence of COVID-19. The findings of this paper reinforced the hypothesis that the serum level of cortisol is associated with severe outcomes in patients with COVID-19 infection.

We found out that an increased cortisol level is prevalent among patients with the severe form of COVID-19 infection. Furthermore, the patients with high serum cortisol levels are most likely at higher risk of developing severe form of COVID-19 and even dying from the disease. Our results demonstrated that the serum cortisol levels were higher among patients with the severe form. Our findings are in an agreement with previous studies. Previously, elevated cortisol levels have been suggested as a potential risk factor for severe outcome and death in COVID-19.[11] Tan et al suggested cortisol as a predictor biomarker rather than other markers related to COVID-19, such as IL-6, CRP and D-dimer.[11] In addition, cortisol, in combination with other markers, can be applied as a prognostic marker of the disease outcome. In line with our study, Ramezani et al also found that patients with more severe form of the disease were more likely to have elevated serum cortisol levels.[24]

To enhance the validity of the results, the studies were classified into two groups, including observational and case report studies. The obtained results for the two types of

studies proved that the circulating cortisol levels significantly increase in patients with severe COVID-19 in comparison with those with mild-to-moderate COVID-19. It should be noticed that in case report studies, all of the examined clinical symptoms were reported in one sample; thus, the obtained results of the combined data of case report studies should be interpreted with caution.

Currently, investigations on the mechanisms of COVID-19 being related to elevated cortisol are limited. The elevation in cortisol levels is an important component of the body's response to stress, triggering adaptive alterations in regulation of the immune system. It has been reported that SARS-CoV might activate an immunogenic response to adrenocorticotropic hormone.[25] On account of the genomic similarity between SARS-CoV-2 and SARS-CoV, a similar mechanism is probably applied, leading to morbidity and mortality through induction of cortisol insufficiency related to the severe form.

The current study has some limitations, including the restricted interpretation of our meta-analysis with the small sample size and lack of reports on adrenal damage during COVID-19 infection in people tested positive for SARS-CoV-2. Moreover, another limitation of the present study was significant heterogeneity among the included studies. To this end, we performed subgroup and meta-regression analyses to explore the source of heterogeneity. Additionally, the relatively small sample size in subgroup analysis could be another limitation of the current research.
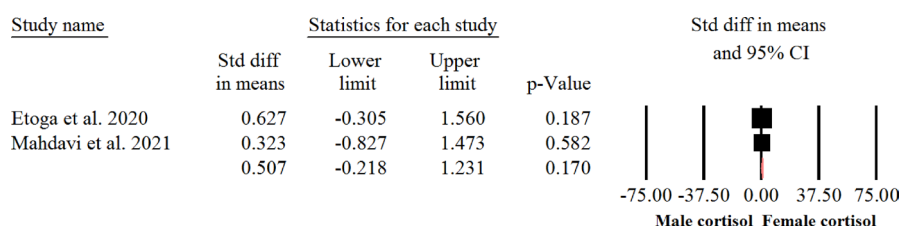
Figure 5 Forest plot detailing subgroup of standardized mean difference and 95% CIs for the relationship between the circulating cortisol level and COVID-19 severity. Studies were classified on the basis of sex (male and female).

In summary, given that the patients' conditions for cortisol response are different, it is too early to mention it as a distinctive biomarker. Regarding this, cortisol, in combination with other markers, may be helpful as a prognostic marker of the disease outcome. Measurements of serum cortisol levels in patients with COVID-19 can provide a new perspective on the proper management of the disease and in the future, can be effective alone or in combination with the other reported prognostic markers associated with the prediction of disease outcome. However, further validation studies are required in this regard. On the other hand, since cortisol has been implicated as the cause of a broad range of mental disorders, the psychological interventions during the illness might be important in reducing and improving the complications and outcome of the disease.

Correction notice This article has been corrected since it was first published. Corresponding author Hossein Chiiti's affiliation has been updated to affiliation 1.

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