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Research Article

Association Between Administration of Corticosteroids and Mortality Among Iranian Patients With COVID-19: A Retrospective Study

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Abstract

Background: According to the evidence, coronavirus disease 2019 (COVID-19) is associated with significant mortality among hospitalized patients. Corticosteroid drugs have had different effects on disease-associated fatality. This study aimed to evaluate the corticosteroid-associated mortality rate and its related risk factors in the southern Iranian population infected by COVID-19.

Methods: A retrospective study was conducted on the adult population aged ≥ 20 years admitted to Shahid Mohammadi hospital in Bandar Abbas, Iran between February 2020 and October 2020. All subjects were confirmed for COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR).

Results: Among 1610 included cases, 150 (9.3%) died. Also, 58.5% and 58.7% of the total hospitalized and mortality cases were male, respectively. The mortality rate in subjects older than 60 years was 2.5 times higher than patients aged 20-40 years, which was statistically significant ($P < 0.001$). The results of logistic regression analysis revealed that age was the most significant risk factor for mortality. The elderly patients (> 60) had nearly ten times higher chance of fatality than patients aged less than 40 years (adjusted odds ratio [aOR]: 9.79, 95% CI: 4.41-21.74). Using corticosteroids independently increased the chance of mortality by 50% (aOR: 1.53, 95% CI: 1.06-2.22). Low oxygen saturation (< 93%) raised mortality rate by more than 3.5 times compared to oxygen saturation ≥ 93% (aOR: 3.67, 95% CI : 2.54-5.31). In addition, ischemic heart disease (IHD) was another remarkable predictor of death (aOR: 2.85, 95% CI: 1.88-4.31).

Conclusion: According to our results, corticosteroids had no benefits for reducing the mortality rates among COVID-19 patients. Further randomized clinical trials are suggested to evaluate the effects of corticosteroids on COVID-19-related mortality.

Keywords: Corticosteroid, COVID-19, Mortality rate, Iran

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Background

Because of the absence of recognized, well-proven effective therapies, the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be a serious global concern. As a result, most countries have been affected, resulting in tremendous stress on healthcare systems (1, 2).

The clinical description of COVID-19 has ranged from asymptomatic or mild to excessively severe pneumonia, mostly causing adult respiratory distress syndrome (ARDS), which is a condition that needs extended mechanical breathing or extracorporeal membrane oxygenation (ECMO) (3,4).

In the pathophysiology of severe COVID-19 disease, the patients' immune response has a fundamental role. It has been observed that the immune response becomes dysregulated in various patients. Evidently, COVID-19 pneumonia is accompanied by increased inflammation and immunosuppression (5). The significant symbol of pulmonary pathology in COVID-19 patients is diffuse alveolar destruction, which is frequently related to the thickening of the alveolar walls with infiltration caused by the inflammatory cells, mainly by macrophages and mononuclear cells (6). It has also been remarked that COVID-19 patients develop

significant pulmonary vascular endothelial cell injury and endothelialitis, connected with intravascular thrombosis and microangiopathy (7,8). COVID-19 disease is mainly correlated with numerous raised inflammatory biomarkers, cytokines, and chemokines, which tend to appear very high in severe cases.

Although many proposed therapies for reducing the inflammatory response are being assessed, there is still a lack of robust, tangible proof of benefit. Corticosteroids have shown positive, beneficial outcomes in overcoming hyper inflammation and ARDS (3, 9-11). Furthermore, they can help as a convenient and affordable treatment choice.

However, corticosteroid use has some well-known adverse effects, like delayed viral clearance, opportunistic infections, and suppressed hypothalamic-pituitary-adrenal axis (12-14). Previous studies performed during Middle East respiratory syndrome (MERS)-CoV and SARS-CoV exhibited delayed viral clearance, opportunistic infections, and hyperglycemia (15-17). Consequently, the positive impact of corticosteroids on COVID-19 patients has been observed in observational studies and randomized controlled trials (RCTs). The RECOVERY trial, one of the first large randomized trials, reported that dexamethasone resulted in decreased 28-day mortality and improved patients' survival rate in severe and critical COVID-19 cases who required supplemental oxygen therapy or mechanical ventilation (18). Additionally, corticosteroids were linked to a lower 28-day all-cause death rate in a prospective meta-analysis of seven RCTs (19).

While the World Health Organization (WHO) initially had advised in contradiction of the corticosteroid therapy, as of September 2, 2020, and after the meta-analysis done by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working group, it now recommends systemic corticosteroids rather than no systemic corticosteroids in order to manage severe and critical COVID-19 patients (19, 20). Moreover, the Surviving Sepsis Guideline on critically ill COVID-19 patients' management also suggests that patients with serious COVID-19 who are on mechanical ventilation and have ARDS, as well as with refractory shock, should take steroids (21).

However, the efficacy and safety of corticosteroids are still being debated due to the lack of RCTs and uncertain observational studies. So, achieving reliable and trustworthy data is essential to further investigate the benefits and side effects of corticosteroids.

Objectives

This study aimed to explore the COVID-19 mortality rates among patients taking corticosteroids in Bandar Abbas, Iran between February 2020 and October 2020.

Materials and Methods

Participants

We conducted a retrospective study consisting of COVID-19 patients aged ≥ 20 years admitted to all departments, including intensive care unit (ICU) in Hormozgan province. COVID-19 infection was confirmed by real-time reverse transcriptase polymerase chain reaction (PCR) (RT-PCR) assay nasopharyngeal swab specimens between Februrary 2020 and October 2020. RT-PCR tests had been performed on specimens from nasopharyngeal swabs using the STANDARD M nCoV Real-Time Detection Kit (SD Biosensor Inc., South Korea). The kit is based on TaqMan probe technology targeting RdRp and E genes. Pregnant women and patients lacking most of the required information were excluded.

Study Design

The patients' data were extracted from the electronic medical records using standardized data collection sheet. We recorded information on age, gender, pre-existing medical conditions, including hypertension, diabetes mellitus (DM), ischemic heart disease (IHD), chronic lung disease (CLD), chronic kidney disease (CKD), malignancy, oxygen saturation, and cigarette smoking.

Statistical Analysis

SPSS software (version 20.0) was used for data analysis. Mean, standard deviation, frequency, and percentages were used to describe the results. Independent *t* test and chi-square test were applied to compare quantitative and qualitative variables, respectively, among the dead and survivor groups. The binary logistic regression model was used to determine the independent role of corticosteroid use and other variables in mortality. A *P* value less than 0.05 was considered as significant level.

Results

Among 1610 confirmed COVID-19 cases, 150 (9.3%) died. Table 1 compares demographics, clinical conditions, and corticosteroid use between the dead and survivor groups. According to Table 1, 58.5% of the hospitalized patients and 58.7% of dead patients were male. Although the male gender had a higher proportion of mortality than females, this difference was not significant. The mean age was markedly higher in the dead group than the survivor group. The mortality rate in subjects older than 60 years was 18.8% and 1.5% among people aged 20-40 years, which was statistically significant ($P<0.001$). The patients who received corticosteroids had a significantly higher mortality rate than patients not taking corticosteroids (12.7% vs. 7.0%) ($P<0.001$). Likewise, the most significant mortality rate was related to cerebrovascular disease (CVD) (33.3%), followed by IHD (25.2%), cancer (22.7%), hypertension (17.9%), and

Table 1. Mortality Rate Based on Demographics, Clinical Conditions, and Taking Corticosteroids Between Dead and Survivor Groups

Variables	Survivor	Dead	*P* Value
Age (y), Mean ± SD	50.38 ± 15.39	64.77 ± 13.27	<0.001
Age categories, No. (%)			<0.001
20-40	474 (98.5)	7 (1.5)	
41-60	562 (92.6)	45 (7.4)	
>60	424 (81.2)	98 (18.8)	
Gender, No. (%)			0.323
Female	665 (91.5)	62 (8.5)	
Male	795 (90.0)	88 (10.0)	
Corticosteroid taking, No. (%)			<0.001
No	881 (93.0)	66 (7.0)	
Yes	579 (87.3)	84 (12.7)	
Diabetes mellitus, No. (%)			<0.001
No	1197 (92.0)	104 (8.0)	
Yes	263 (85.1)	46 (14.9)	
Hypertension, No. (%)			<0.001
No	1199 (92.8)	93 (7.2)	
Yes	261 (82.1)	57 (17.9)	
Ischemic heart disease, No. (%)			<0.001
No	1309 (93.0)	99 (7.0)	
Yes	151 (74.8)	51 (25.2)	
Cerebrovascular disease, No. (%)			<0.001
No	1448 (91.0)	144 (9.0)	
Yes	12 (66.7)	6 (33.3)	
Asthma, No. (%)			0.713
No	1419 (90.7)	145 (9.3)	
Yes	41 (89.1)	5 (10.9)	
Chronic lung disease, No. (%)			0.150
No	1442 (90.8)	146 (9.2)	
Yes	18 (81.8)	4 (18.2)	
Chronic kidney disease, No. (%)			0.014
No	1398 (91.1)	137 (8.9)	
Yes	62 (82.7)	13 (17.3)	
Cancer, No. (%)			0.029
No	1443(90.9)	145 (9.1)	
Yes	17(77.3)	5 (22.7)	
O2 saturation < 93%, No. (%)			<0.001
No	1120 (94.7)	63 (5.3)	
Yes	340 (79.6)	87 (20.4)	
Cigarette smoking, No. (%)			0.064
No	1434 (90.9)	144 (9.1)	
Yes	26 (81.3)	6 (18.8)	

Table 2. Comparison of Crude and Adjusted Odds Ratio of Different Variables for Mortality

Variables	Death		*P* Value
	Crude OR (95% CI)	Adjusted OR (95% CI)	
Age categories			
20-40	1.0	1.0	
41-60	5.42 (2.42-12.13)	4.46 (1.97-10.07)	<0.001
>60	15.65 (7.19-34.07)	9.79 (4.41-21.74)	<0.001
Gender			
Female	1.0		
Male	1.18 (0.84-1.67)	-	
Corticosteroid taking			
No	1.0	1.0	
Yes	1.93 (1.38-2.71)	1.53 (1.06-2.22)	0.023
Diabetes mellitus			
No	1.0		
Yes	2.01 (1.38-2.92)	-	
Hypertension			
No	1.0		
Yes	2.81 (1.97-4.01)	-	
Ischemic heart disease			
No	1.0	1.0	
Yes	4.46 (3.06-6.51)	2.85 (1.88-4.31)	<0.001
Cerebrovascular disease			
No	1.0	1.0	
Yes	5.02 (1.85-13.59)	2.98 (0.98-9.00)	0.053
Asthma			
No	1.0		
Yes	1.19 (0.46-3.06)	-	
Chronic lung disease			
No	1.0		
Yes	2.19 (0.73-6.57)	-	
Chronic kidney disease			
No	1.0		
Yes	2.14 (1.14-3.99)	-	
Cancer			
No	1.0		
Yes	2.92 (1.06-8.05)	-	
O2 saturation < 93 %			
No	1.0	1.0	
Yes	4.54 (3.21-6.43)	3.67 (2.54-5.31)	<0.001
Cigarette smoking			
No	1.0		
Yes	2.29 (0.93-5.67)	-	

Reference was survivors.

DM (14.9%). A low oxygen saturation (<93%) increased the fatality rate by about four times compared to normal oxygen saturation ($P<0.001$).

Table 2 provides information about crude and adjusted odds ratio (aOR) of different variables, including corticosteroid taking, regarding the mortality rate. Logistic regression analysis showed that age was the most significant risk factor of mortality. The OR of fatality rate in patients older than 60 years was nearly 10 times higher than people aged less than 40 years (aOR: 9.79, 95% CI: 4.41-21.74). The second influential factor in mortality was a low oxygen saturation (<93%), so that it raised mortality rate by more than 3.5 times compared to oxygen saturation ≥93% (aOR: 3.67, 95% CI: 2.54-5.31). Another remarkable factor was the IHD (aOR: 2.85, 95% CI: 1.88-4.31). Also, using corticosteroids increased the chance of

mortality by 50% (aOR: 1.53, 95% CI: 1.06-2.22).

Discussion

In this study, we investigated the effect of systemic corticosteroids on mortality rates in 1610 COVID-19 patients in the hospitals of Hormozgan province in Iran. Corticosteroids were utilized in 41.18% of the cases. The results showed that using corticosteroids was not beneficial in reducing the mortality rates of COVID-19 patients.

No effective antiviral therapy has been discovered since the outbreak of the new SARS-CoV-2 virus. As a result, COVID-19 patients are mostly treated with symptomatic therapy, mainly focusing on supportive care and oxygen therapy, based on previous SARS and MERS treatment experiences.

Since corticosteroids firstly were suggested as a treatment strategy for ARDS (22, 23), there has been a debate in the scientific community over whether COVID-19 patients should be adjunctively treated with them. The Guangzhou retrospective study on SARS suggested that corticosteroids could reduce mortality in critical patients (24). Likewise, a RCT found that early dexamethasone therapy could lower overall mortality in individuals with established moderate-to-severe ARDS (11).

At the beginning of the COVID-19 pandemic, physicians were advised to take caution in prescribing corticosteroids, as they may cause prolonged viral shedding and decreased viral clearance (25). However, prescribing corticosteroids became increasingly popular after a study conducted in Wuhan, China, revealed that using methylprednisolone decreased the risk of death among COVID-19 patients with ARDS and suggested that corticosteroids may be beneficial for patients who develop ARDS (26). Nevertheless, this study suffered some critical limitations, including that it was conducted at a single-center hospital with limited sample size, and the corticosteroid therapy was assessed in only a small sample size cohort of ARDS patients.

Studies have proposed that COVID-19 invasion prompts immunological and inflammatory responses, causing immune cells to release several pro- and anti-inflammatory cytokines, as well as significantly higher levels of inflammatory markers (27). The excessive release of cytokines leads to severe alveolar and airway damage, causing extensive destruction to the pulmonary vascular endothelial and alveolar epithelial cells, increased pulmonary vascular permeability, pulmonary edema, and hyaline membrane formation (28).

Pulmonary histological examinations from a COVID-19 patient revealed diffuse alveolar damage with cellular fibromyxoid exudates, hyaline membrane formation, and pulmonary edema, indicating ARDS. Furthermore, the biopsy samples from this study also revealed that the pathological hallmarks of COVID-19 greatly resemble those seen in MERS-CoV and SARS-CoV infections (29). These results suggest that COVID-19 infection is usually associated with increased immune and inflammatory responses, and immune factor concentrations are possibly linked with disease severity (30).

Corticosteroids are classic immunosuppressants that accomplish critical physiological processes, such as inhibiting the immunological response and in force as anti-inflammatory drugs to decrease systemic inflammation, all of which are critical in avoiding or delaying the development of pneumonias (31, 32).

Our finding showed that corticosteroid therapy was an independent factor for higher mortality rate. Although the Randomized Evaluation of COVID-19 therapy (RECOVERY) trial showed that treatment with corticosteroid was linked with lower mortality in severe and critical COVID-19 patients, we could not observe a similar association in our study (18). Moreover, the prospective meta-analysis by WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, consisting of seven randomized trials, revealed that patients who received corticosteroids had a lower mortality rate than those who did not receive corticosteroids, again contradicting our findings (19).

Our findings indicated that corticosteroid therapy had no favorable impact on the endpoint of death among COVID-19 patients, which is consistent with the results of a previous study conducted on MERS-CoV infection. In a multicenter study of 309 MERS patients, the crude mortality was higher in the group treated with corticosteroids, although later, the adjusted mortality showed no difference among the two groups (15). Moreover, the results from a multicenter RCT of patients with persistent ARDS did not support the routine use of corticosteroids. They even found an increased risk of mortality when treatment began late in the course of the disease (33).

This study had some limitations. The major limitation of the study is its retrospective aspect; further RCTs should be conducted to validate our results. Also, the findings are only applicable to centers with similar settings and COVID-19 admission volumes due to the single-center nature of the study. Therefore, meta-analyses using the findings of this study and other similar studies are required.

In conclusion, our study showed that the use of corticosteroids showed no evidence of benefit for decreasing the mortality rates among COVID-19 patients. So, we do not suggest using corticosteroids regularly for this purpose outside of a trial setting.

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Authors' Contribution

Study concept and design: KS, Acquisition of data: AS, Analysis and interpretation of data: AR & MK, Drafting of the manuscript: AA, Critical revision of the manuscript for important intellectual content: SKM, Statistical analysis: MM, Administrative, technical, and material support: HKZ, Study supervision: MK All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interests

The authors declare that they have no competing interests.

Ethical Approval

The study protocol was reviewed and approved by the Ethics Committee of the Hormozgan University of Medical Sciences (Code: IR.HUMS.REC.1399.501), and it was conducted in agreement with the Declaration of Helsinki. The retrospective design of the study waived the need for informed consent from the patients. Patients' discretion was observed, and the analysis was performed anonymously.

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