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Original Article

Effect of treatment regimens in severe COVID pneumonia at an Indian tertiary care hospital: An observational, real-world study

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ABSTRACT

Background: Corticosteroids have attracted attention as a treatment option for severe Coronavirus disease (COVID-19). However, published data on steroid therapy is debatable, and real-world data is lacking. This study evaluated the effect of treatment regimens, especially Pulse steroid therapy (Injection Methyl Prednisolone 250 mg iv once a day for three days) in severe-COVID-19 pneumonia at an Indian tertiary care hospital.

Methods: This observational cross-sectional study included severe COVID-19 pneumonia patients aged >18 years, requiring assisted ventilation. As part of the hospital protocol, patients received either pulse steroid therapy, remdesivir or tocilizumab in addition to the recommended steroid doses i.e., injection of dexamethasone 6 mg iv once a day. The association of factors and treatment regimens to patient outcomes was evaluated.

Results: Data of eighty-three patients were assessed, majority being above 60 years (n = 30, 36.14%) and males (n = 45/83, 54.21%). The commonest comorbidities were hypertension (n = 26), diabetes (n = 23) and obesity (n = 19), fifty-five patients (66.26%) reported at least one comorbidity. Sixty-one patients (73.49%) had received pulse steroid regimen, forty-eight patients (57.83%) were administered remdesivir-based regimen while twelve patients (14.46%) had received tocilizumab treatment. 54.1% patients managed with pulse steroid regimens were discharged after treatment, statistically similar to remdesivir-managed subgroup (62.5%, $p > 0.05$). On sub-group analysis, pulse steroids showed better outcomes in young males with no comorbidities. No comorbidity had significant relationship with patient outcomes ($p > 0.05$).

Conclusion: Pulse steroid therapy is an effective therapy in management of patients with severe COVID-19 pneumonia in a real-world setting, with better outcomes in young males

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without comorbidities. Pulse steroids can be considered a viable option for severe-COVID-19 pneumonia management.

Introduction

In March 2020, the World Health Organization (WHO) declared COVID-19 disease a global pandemic. It will not be wrong to say that the pandemic, caused by the severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2) strain, wreaked havoc, leading to more than 236 million confirmed cases and more than 4.8 million deaths globally, as of October 2021.[1] As the COVID-19 pandemic spread across all parts of the world, the hospitals and intensive care units were overwhelmed with a heavy load of severe cases, and with limited knowledge of the disease, managing the severe cases was a challenge for all clinicians. In India, this was an even bigger challenge with the massive population completely exhausting the hospital beds and the lack of clarity on managing severe COVID-19 pneumonia adding to the difficulty in managing these cases.

Many pharmacological therapies (for example remdesivir, tocilizumab) have been administered to patients suffering from severe COVID-19 pneumonia, despite the dearth of evidence supporting their efficacy. In addition, the supply of promising drugs like remdesivir was also challenging to fulfil, and hence it becomes imperative to look at other options for managing severe COVID-19 patients. It was not surprising to note the attention attracted by corticosteroids, because it has been used as an anti-inflammatory agent for a long time. Clinicians, particularly intensivists, have used corticosteroids in patients suffering from acute respiratory distress syndrome and septic shock to improve outcomes.[2] In addition, corticosteroids are easily available and an inexpensive option.

At the onset of the COVID-19 pandemic, guidelines gave a mixed recommendations on corticosteroid usage. Guidelines from the Infectious Disease Society of America (IDSA), published in April 2020, stated a weak recommendation for steroid use, except in cases of COVID-19 and acute respiratory distress syndrome managed in a clinical trial.[3] The WHO guideline made a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 h) for 7–10 days in patients diagnosed with severe and critical COVID-19 pneumonia. In addition, WHO also made a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19.[4]

In the real world, clinicians faced with the challenge to manage patients dying due to severe COVID-19 pneumonia used various and often higher than recommended doses of steroids.[5,6] Scientific publications also recommended a short course of pulse i.e., Injection Methyl Prednisolone 250 mg iv once a day for three days, to patients with severe COVID-19.[7] There is no doubt that real-world data are the need of the day to give clarity to clinicians across the globe with regards to the use of pulse steroid therapy in severe COVID-19 cases. Hence, we evaluated the efficacy of various drug regimens, including a pulse-steroid-based regimen, in severe COVID-19 pneumonia cases, at a tertiary care Indian hospital. With the threat of another 'wave' of COVID-19 cases looming, this data will help in guiding the clinicians globally with respect to steroid use in the pandemic-stricken population.

Material and methods

This retrospective observational cross-sectional study was conducted at a 970-bedded tertiary care hospital in India. The study included patients with pneumonia and with severe COVID-19 over the age of 18 years, confirmed by positive real-time reverse transcription polymerase chain reaction for SARS-CoV2 and requiring invasive or non-invasive ventilation. Patients were not randomly selected and data available of all severe COVID-19 cases were screened. The study period was from 1st March 2021 to 31st May 2021, i. e., during the second wave of COVID 19 pandemic in India. The strain analysis for Coronavirus was not done, but the strain most commonly noted during this period in India was the delta variant. Adult patients with severe COVID-19 in the study were patients with dyspnoea and with a respiratory rate of 30 or more breaths per minute, a SpO2 of less than 92%, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao2:Fio2) (P/F ratio) of less than 300 mm Hg, or infiltrates in more than 50% of the lung fields. All patients were of severe COVID-19 pneumonia on high flow nasal cannula/non-invasive ventilation/mechanical ventilation. The main exclusion criteria included the lack of complete relevant data of patients with severe COVID-19, patients who had dissented from medical management, mortality in the first 24 h of admission, patients in palliative care, or with a life expectancy lower than six months. Informed consent was obtained from all patients/next of kin. The study received hospital ethics committee approval before it was initiated (EC Number: ECR/1313/Inst/WB/2019.)

As part of the hospital protocol, the patients enrolled in the study had received either pulse steroid therapy (Injection Methyl Prednisolone 250 mg iv once a day for three days), remdesivir, or tocilizumab. A pulse dose of steroids was given to patients with severe COVID pneumonia with rapid worsening of respiratory failure despite optimum management. All factors including high c-reactive protein (CRP) values and deteriorating P/F ratio were taken into consideration while starting pulse steroid therapy. Prior clearance of the ethical committee was sought and obtained as a life-saving measure. Patients at the hospital who received pulse steroid therapy were administered an injection of dexamethasone 6 mg once a day pre and post pulse steroid therapy for a total duration of steroids of ten days. Patients on Remdesivir were on the usual recommended doses of steroids,

i.e., injection of dexamethasone 6 mg intravenously. Remdesivir was started and given for a period of 5 days, in patients with severe COVID-19 pneumonia reporting symptoms onset of less than 7 days duration. The patients who showed rapid worsening of respiratory distress despite initiation of steroids and had markedly elevated inflammatory markers (CRP≥75 mg/L) were given a single dose of intravenous Tocilizumab 8 mg/kg.

The baseline data of the enrolled patients included demographic details like age, gender, and comorbidities. The baseline investigations included the routine investigations along with other investigations usually conducted on severe COVID-19 cases in the hospital as protocol. These were interleukin-6 (IL-6) levels, CRP, D-dimer, Serum ferritin, Serum Procalcitonin and lactate dehydrogenase levels. The outcomes of the patients were noted down, i.e., either death or discharge.

The analysis was done to evaluate the association of numerous factors and treatment regimens to patient outcomes. Data were entered in Microsoft Excel and analyzed using SPSS (Version 26.0). The various patient factors included age, gender, and comorbidities while the treatment factors included the duration between treatment administration and patient outcome. The associations were evaluated using univariate analysis by Chi-square test, taking $p < 0.05$ as statistically significant (Flowchart).

Results

Data of eighty-three patients fulfilling the screening criteria were evaluated in the study. The majority of the patients were above the age of 60 years (n = 30, 36.14%), followed by 51–60 years' age group (n = 23, 27.71%) and 41–50 years (n = 17, 20.48%). The majority of the enrolled patients were males (n = 45/83, 54.21%). Fifty-five of the enrolled patients (66.26%) were found to be suffering from at least one comorbidity. The commonest comorbidities were hypertension (n = 26), diabetes (n = 23), obesity (n = 19), chronic respiratory disorder (n = 8), and hypothyroidism (n = 6). Majority of the patient outcomes, i.e., either death or discharge were noted between 6 and 10 days (n = 29) or 11–15 days (n = 26) after treatment initiation.

Sixty-one of the eighty-three patients (73.49%) had received a pulse steroid regimen for managing severe COVID-19 pneumonia, and forty-eight patients (57.83%) were administered a remdesivir-based regimen while twelve patients (14.46%) had received tocilizumab treatment. Table 1 below gives a representation of a number of patients with various therapies, while Table 2 shows the patient outcomes with various treatment regimens. As treatment regimens, the majority of patients had received only pulse steroids, followed by a combination of remdesivir plus pulse steroids, and then remdesivir alone (Table 1).

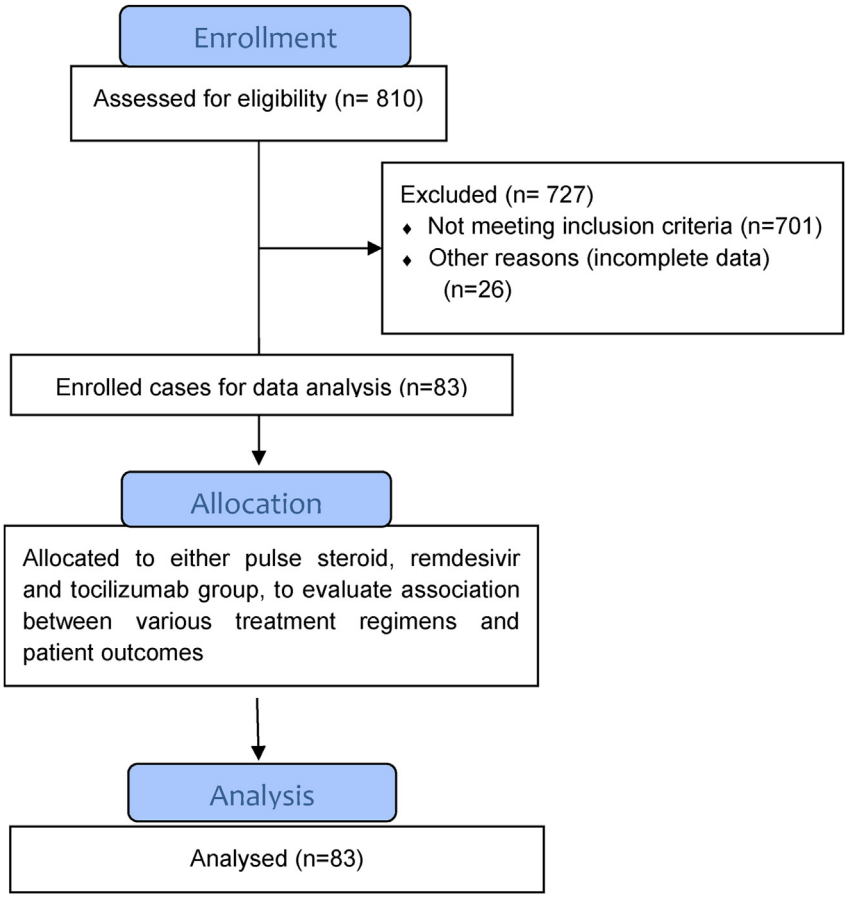
The majority of deaths occurred in the >60 years age group, and this was a statistically significant finding ($p < 0.05$). The deaths in both male (n = 21) and female (n = 15) subgroups were statistically comparable ($p > 0.05$). Overall, the presence of comorbidities was not significantly associated with patient outcomes ($p > 0.05$). On assessing the association of individual comorbidities with patient outcomes, none of the comorbidities had a significant relationship ($p > 0.05$). Table 3 illustrates the association findings between numerous factors and patient outcomes.

Discussion

The treatment options for severe COVID-19 infections remain limited. Besides the supportive therapy, the treatment regimens adopted globally include remdesivir, tocilizumab, and steroid-based management. As summarized in various published review articles, remdesivir may have only modest benefit in time to recovery in patients suffering from severe disease but has shown no significant benefit in mortality or other clinical outcomes.[8] The largest trials evaluating the effect of Tocilizumab in COVID-19 reported a modest mortality advantage and betterment in outcomes; nevertheless, adaptive trials are at risk of bias which can impact non-mortality outcomes. The cause for mixed results is uncertain, and reasons involve earlier trials had insufficient power to identify a modest benefit, the requirement for corticosteroid use, or early use in critical illness is necessary for tocilizumab to be efficient.[9,10] Corticosteroids are the only therapeutic agents which have shown a clear mortality benefit in severe COVID-19 pneumonia management. Seven RCTs have assessed treatment with steroids in critically ill patients, evaluating various steroid formulations like dexamethasone, methylprednisolone, and hydrocortisone with promising outcomes.[11] However, the dearth in real-world data is evident with regards to the effect of various treatment regimens in severe COVID-19 pneumonia. In our study, we have tried to present the real-world findings of the severe COVID-19 pneumonia management from a tertiary care center in India, with regard to the mortality and discharge outcomes.

The majority of the severe COVID-19 cases were found to be of the elderly age group. There is enough scientific evidence and clinical experience to show that elderly patients are at risk of a more severe form of COVID-19 infection.[12] In addition, the increased comorbidities in the elderly age group add to the poor patient outcomes.[13] Hence, the majority proportion of elderly patients in the study died. The data analysis of patients with severe COVID-19 revealed that almost three-fourth of patients had received a pulse-steroid regimen in the hospital, while about half of the patients had received Remdesivir based regimen. There have been various concerns raised regarding the adverse effects of steroid therapy, but evidence suggests that severe COVID-19 patients who have reached early-70s can be considered optimal patients who can have tolerable adverse effects. Pulse therapy with tapering of steroid dosage after betterment in patient condition can help avoid severe adverse effects.[14]

For therapy, dexamethasone was administered in the study at a dose of 6 mg daily for 10 days. Based on available published evidence, if dexamethasone is unavailable, it is rational to use other glucocorticoids at equivalent doses (e.g., total daily doses of methylprednisolone 32 mg, prednisone 40 mg, or hydrocortisone 150 mg).[15] Mechanism of steroid effect in COVID-19 cases have been highlighted in various published data. In COVID-19-related severe acute respiratory syndrome, viral



Flowchart: Data analysis and inclusion for patients in the study.

escape of cellular immune response as well as the cytokine storm is crucial in pathophysiology and clinical outcomes. There is severe lung inflammation which causes acute respiratory distress syndrome, respiratory failure, and death.[16] Corticosteroids have substantial anti-inflammatory as well as anti-fibrotic effects, which may be a role in lowering pulmonary inflammation, particularly in severe pneumonia in progressed stages of COVID-19 disease.[2,17] Nevertheless, the use of corticosteroids may decrease the immunological response, pathogen clearance, as well as promote viral replication, its downregulation effect may last on the proinflammatory cytokines, subsequently averting the extensive cytokine response and stimulating the resolution of pulmonary as well as systemic inflammation in pneumonia.[18,19]

More than half of the patients managed with pulse steroid regimens were discharged after treatment, which was like the outcome noted in those treated with remdesivir-based regimens in the study. The response in patients treated with Inj Tocilizumab was not good as these patients likely had poorer prognosis because of a surge in IL-6 and associated cytokine storm. Our findings suggested a statistically comparable outcome between groups of severe COVID-19 pneumonia patients managed with either treatment regimen. Hence, it can be said that steroid-based regimens had mortality benefits like remdesivir and tocilizumab. However, on subgroup analysis, it was noted that pulse steroids showed better results in young males with no comorbidities. This is important as the availability of remdesivir, and tocilizumab was a major concern when the last severe COVID-19 spike was experienced in India in April–May 2021. There was an increase in the cost as well as black marketing of these drugs. On the other hand, steroids are much cheaper and are freely available in all parts of the country. With similar outcome findings and mortality advantages according to scientific evidence, this can be a point of consideration if there is another COVID-19 spike in the future. Young obese females fared the worst with respect to outcomes, irrespective of the form of management utilized. Though the reason is difficult to explain, a similar finding has been noted in another research from the UK by Peters et al.[20] The study found that higher BMI was associated

Table 1 – Patient distribution by various therapies administered.

Therapy administered	Total patients	Death	Discharge
Only pulse steroids	28	13 (46.43%)	15 (53.57%)
Only remdesivir	17	6 (35.29%)	11 (64.71%)
Only tocilizumab	3	2 (66.67%)	1 (33.33%)
Remdesivir + pulse steroids	25	10 (40%)	15 (60%)
Tocilizumab + pulse steroids	3	3 (100%)	0
Tocilizumab + remdesivir	1	0	1 (100%)
Pulse steroids + tocilizumab + remdesivir	5	2 (40%)	3 (60%)

Table 2 – Various treatment regimens for COVID cases and patient outcomes.

	Death	Discharge
Pulse steroid regimen (n = 61)	28 (45.9%)	33 (54.1%)
Remdesivir (n = 48)	18 (37.5%)	30 (62.5%)
Tocilizumab (n = 12)	7 (58.33%)	5 (41.67%)

Table 3 – Association between various patient or treatment factors and patient outcomes.

	Death	Discharge	P value
Age group			
21–30 years (n = 6)	0	6 (100%)	**<0.01**[a]
31–40 years (n = 7)	2 (28.58%)	5 (71.42%)	
41–50 years (n = 17)	5 (29.42%)	12 (70.58%)	
51–60 years (n = 23)	9 (39.14%)	14 (60.86%)	
>60 years (n = 30)	20 (66.67%)	10 (33.33%)	
Patient's gender			
Males (n = 45)	21 (46.67%)	24 (53.33%)	0.66
Females (n = 38)	15 (39.48%)	23 (60.52%)	
Comorbidity status			
Comorbidities present (n = 55)	27 (49.09%)	28 (50.91%)	0.16
Comorbidities absent (n = 28)	9 (32.15%)	19 (67.85%)	
Comorbidity type			
Hypertension (n = 26)	14 (53.84%)	12 (46.16%)	0.23
Diabetes mellitus (n = 23)	12 (52.17%)	11 (47.83%)	0.33
Obesity (n = 19)	12 (63.16%)	7 (36.84%)	0.07
Chronic respiratory disorder (n = 8)	5 (62.5%)	3 (37.5%)	0.28
Coronary artery disease and cardiac dysfunction (n = 5)	3 (60%)	2 (40%)	0.65
Duration between treatment Initiation and outcome			
0 day (n = 5)	5 (100%)	0	**0.14**[a]
1–5 days (n = 29)	15 (51.72%)	14 (48.28%)	
6–10 days (n = 26)	9 (34.62%)	17 (65.38%)	
11–15 days (n = 15)	5 (33.33%)	10 (66.67%)	
16–20 days (n = 3)	2 (66.67%)	1 (33.33%)	
>20 days (n = 5)	0	5 (100%)	

[a] P<0.05 considered significant by Chi-square test.

with a stronger risk of COVID-19 mortality in women than men; the women-to-men ratio of hazard ratios was 1.20. The study also could not explain this, but this can be a topic of exploration in future research.

WHO guideline, which made a recommendation for systemic steroid usage in severe and critical COVID-19 cases, was triggered in June 2020 by the dissemination of the preliminary report of the RECOVERY trial. The study suggested that dexamethasone 6 mg given once a day for up to a period of 10 days in comparison to usual care decreased the 28-day mortality (482/2104 [22.9%] of patients administered dexamethasone versus 1110/4321 [25.7%] of patients given the usual care). The age-adjusted rate ratio [RR] was noted to be 0.83 (95% confidence interval [CI] 0.75–0.93) which was a significant finding. The authors had also mentioned that this benefit was not noted in those patients not on respiratory support.[21] The other studies evaluating the treatment regimens in severe COVID-19 were RCTs which did not portray a picture identical to the real-world setting. There are limitations of RCTs which include the presence of inclusion and exclusion criteria. However, in the real world, patients cannot be excluded. Plus, there are issues of generalizability with RCTs. Therefore, it is important for real-world evidence to supplement data from RCTs, and positively bridge the gap between the controlled nature of an RCT and the harsh realities of the real world.[20]

The study had a few limitations. Since it was a real-world data analysis, a strict screening criterion was not followed, besides the inclusion of severe COVID-19 cases. Confounding factors were not considered in various treatment subgroups, and propensity matching was not done for analysis. In addition, this was a single center study with limited sample size. However, this study lays a strong foundation for future real-world studies, especially from Indian hospitals.

Conclusion

Steroid-based regimens provided similar mortality benefits in comparison to other treatment regimens in patients suffering from severe COVID-19 pneumonia in the real-world setting, with better results in young males with no comorbidities. Pulse steroids can be considered a viable option for severe COVID management, especially in future instances of severe COVID-19 spikes.

Disclosure of competing interest

The authors have none to declare.

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REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Available online at: https://covid19.who.int/. Accessed October 5, 2021.
2. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: evidence and hope during the pandemic. *JAMA*. 2020;324(13):1292–1295.
3. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis*. 2020:ciaa478.
4. World Health Organization. Corticosteroids for COVID-19. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed October 6, 2021.
5. Papamanoli A, Yoo J, Grewal P, et al. High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia. *Eur J Clin Invest*. 2021;51(2), e13458.
6. Pinzón MA, Ortiz S, Holguín H, et al. Dexamethasone vs methylprednisolone high dose for COVID-19 pneumonia. *PLoS One*. 2021;16(5), e0252057.
7. Dolci G, Cassone G, Venturelli F, et al. High-dose glucocorticoids pulse-therapy for beta-coronaviridae pneumonia: a systematic

literature review and case-series of coronavirus disease-2019. *Clin Exp Rheumatol*. 2021;39(5):1119–1125.
8. Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoğlu U. Severe COVID-19 pneumonia: pathogenesis and clinical management. *BMJ*. 2021;372:n436.
9. The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with covid-19. *N Engl J Med*. 2021;384:1491–1502.
10. Sterne JAC, Murthy S, Diaz JV, et al., WHO rapid evidence appraisal for COVID-19 therapies (REACT) working group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA;324:1330-1341.
11. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80(6):639–645.
12. Perrotta F, Corbi G, Mazzeo G, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res*. 2020;32(8):1599–1608.
13. Ro S, Nishimura N, Imai R, et al. Identification of patients with COVID-19 who are optimal for methylprednisolone pulse therapy. *Multidiscip Respir Med*. 2021;16(1):781.
14. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. *Drugs*. 2020;80:1267–1292.
15. Kim AY, Gandhi RT. COVID-19: management in hospitalized adults. UpToDate https://www.uptodate.com/contents/covid-19-management-in-hospitalized-adults. Accessed February 5, 2022.
16. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395:473–474.
17. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet*. 2020;395:683–684.
18. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med*. 2020;46:854–887.
19. Nallamothu BK, Hayward RA, Bates ER. Beyond the randomized clinical trial: the role of effectiveness studies in evaluating cardiovascular therapies. *Circulation*. 2008;118:1294–1303.
20. Peters SAE, MacMahon S, Woodward M. Obesity as a risk factor for COVID-19 mortality in women and men in the UK biobank: comparisons with influenza/pneumonia and coronary heart disease. *Diabetes Obes Metabol*. 2021;23(1):258–262.
21. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med*. 2021;384(8):693–704.