Original paper

Retrospective Study of Early Use of Remdesivir in Patients with Severe COVID-19 (Single Center Experience)

Aymen Hasan Ali[1], Karim Al-Naffi[2]

1 Imam Al-Hussain Medical city, Kerbala, Iraq.
2 Department of Internal Medicine, College of medicine, University of Kerbala, Kerbala, Iraq.

Article information:

Received: 2023-04-16
Accepted: 2022-08-01
Vol. 16, No. 1, Aug, 2023.

Correspondence: Aymen Hasan
Email: aymen4329@gmail.com

Abstract

Background: Remdesivir is the first treatment for COVID-19 to receive FDA approval. On October 22. 2020, the antiviral drug Remdesivir was approved to treat COVID-19 patients requiring hospitalization.
Objectives of the study: To compare the effect of timing of Remdesivir administration on the duration of hospitalization and clinical outcome of hospitalized patients with severe COVID-19 in Imam Al-Hussain medical city, those who received Remdesivir early; in the first week, with others who received it in the second week of the onset of the symptoms.
Patients and methods: A retrospective study was done in Imam al-Hussain medical city in Karbala province. The data was collected from 139 patients' registry (84 male&54 female) with severe COVID-19 infection who admitted to the isolation wards, 68(48.6%) received Remdesivir in the first week, and 71(51.1%) received it in the second week from the onset of symptoms. A comparison was made between the two groups regarding the clinical outcome and duration of hospitalization.
Result: During the first week from the onset of the symptoms, about 48.9% of patients with severe infection received Remdesivir, 95.6% of them improved, and 4.4% died. The median time of recovery was six days. About 51.1% received Remdesivir during the second week, 84.5% improved, and 15.5% died. The median time of recovery was 8.5 days.
Conclusions: The case fatality rate was lower in patients who received Remdesivir during the first week from the onset of symptoms than patients who received treatment in the second week. Patients in the first group recovered substantially faster than those in the second one.
Key words: COVID-19, Remdesivir.

Introduction

After the first reported outbreak in Wuhan, China, Betacoronavirus SARS-CoV-2 (COVID-19) started to spread worldwide [(1)]. Coronavirus is an enveloped positive-sense RNA virus with spike-like projections on the surface that appear crown-like under an electronic microscope; therefore, it is called "coronavirus" [(2)]. In the past two decades, there were two events where a severe disease caused by the beta coronavirus was transmitted from animals to humans. The first one was in 2002– 2003, and it was the cause of severe acute respiratory syndrome coronavirus (SARS) in China and Hong Kong [(3)]. A decade later, in 2012, the other one was responsible for the Middle East respiratory syndrome coronavirus (MERS-CoV), which appeared in Saudi Arabia [(4)].

On December 31, 2019, the World Health Organization (WHO) was informed of the emergence of cases of pneumonia of unidentified etiology noticed in Wuhan city, China. A few days later, another 44 cases were reported by the health authorities in China before a novel coronavirus (SARS-CoV2, which seems to be originated from a seafood market in Wuhan city) was isolated from patients [(5)]. The outbreak with coronavirus in late 2019 was highly infectious, with mortality reaching 2.3% [(6)]. About 80.9% of patients with mild to moderate symptoms showed a better prognosis, while patients with severe symptoms showed a significant increase in mortality that reaches 49% in severely ill patients [(7)].

The first reported case in Iraq was on February 24, 2020, for the Iranian student in Al-Najaf city, south of Baghdad [(8)], and it was started to rise in June 2020 [(9)].

The mean incubation period of COVID-19 is about 5.2 days [(10)]. Although case definitions typically rely on 14 days following exposure, mostly around four to five days [(11)]. COVID-19 is thought to be transmitted mainly by close contact from person to person, when a person cough, sneeze, sing, talk, or breathe via respiratory droplets [(12)]. Recent findings revealed the presence of SARS-COV-2 in stool samples [(13, 14)]. These findings suggest the fecal-oral route in transmission as with enteroviruses [(15)]. The virus could also be transferred from asymptomatic persons who have the infection. Re-infection with the virus was reported worldwide [(16)].

Risk factors include adults aged≥60 years and those with chronic underlying conditions, like diabetes, cardiovascular and cerebrovascular diseases [17]**.** Mortality from COVID-19 appeared to be higher in patients with diabetes, cardiovascular diseases, and hypertension, and those who need invasive mechanical ventilation [18]**.**

COVID-19 was also reported in children under 15 years; however, the cases were fewer than adults [19]. Most children infected with COVID-19 have had mild symptoms with a good prognosis; they were afebrile, and pneumonia did not observe [20].

Clinical symptoms are varied. Patients have upper respiratory tract symptoms in the mild form, these include sore throat, fever, dry cough, rhinorrhea, myalgia, headache, or malaise [21]. Loss or change of taste and, or smell, in addition to diarrhea which can be the initial manifestation of infection [22]. In moderate form, patients present with lower respiratory symptoms such as dyspnea or tachypnea in children and productive cough [19]**.** In severe form, patients presented with fever associated with severe dyspnea, respiratory distress, hypoxia (SpO2 < 94 % on room air), and tachypnea (> 30 breaths/min). Cyanosis may occur in children. The critical form includes patients with respiratory failure who require mechanical ventilation, shock, and other organ failures that require intensive care monitoring and therapy [23]**.** Renal involvement is also reported that varies from mild proteinuria [24] to acute renal injury, which often requires dialysis, possibly using cytokine removal approaches [25]. About 20% of patients in intensive care units need renal replacement therapy [26]. Other involvements are shown in figure (1) [27]**.**

COVID-19 is associated with destructive inflammatory reactions. Many pro-inflammatory cytokines were released, leading to a "cytokine storm." One of the cytokine storm complications is lung injury that can cause acute lung injury or acute respiratory distress syndrome (ARDS) [28]. The latter mechanism in patients with COVID-19 is not entirely assumed; the excessive formation of pro-inflammatory cytokines could be one of the main causative factors [19, 29]**.** Numerous research investigating the cytokine profiles recommended its direct correlation with multi-organ failure, lung injury, and bad prognosis [30].

Diagnosis of acute COVID-19 infection depends on identifying either viral RNA or viral antigens **(31)**. As the test for SARS-CoV-2 identification, real-time quantification RT-PCR is the routine confirmation test suggested by WHO [32]**.** Nasopharyngeal swabs were also used as the gold standard, with pooled nasal and throat swabs being provided the highest sensitivity and high positive predictive values (97% of each), followed by saliva (85%), nasal swabs (86%), and throat swabs (68%) [33]**.**

Antigen tests identify viral proteins offering fast results [34]. Although antigen tests can offer fast performance, unfortunately, they are less sensitive than most nucleic acid-based assays [35]. Antigen tests identify the existence of viral proteins and offer fast results [36]. Antigen tests can offer fast performance; unfortunately, they are less sensitive than most nucleic acid-based assays [35]. The serologic tests are used primarily to indicate previous exposure to the virus [37]. IgM antibodies can be detected after five days post-infection, reaching their highest level through weeks 2 to 3; in contrast, IgG is detectable after two weeks of symptom onset [37, 38].

Numerous biomarkers are being useful in monitoring COVID-19 infection. These include C-reactive protein, interleukin-6, serum amyloid A, D-dimer, lactate dehydrogenase, neutrophil-to-lymphocyte ratio, renal biomarkers, cardiac troponin, platelet, and lymphocytes count. All these biomarkers, except (Lymphocytes and platelet), showed substantially elevated levels in patients with severe complications. Both lymphocytes and platelet count exhibited a significant reduction in severely ill patients [39].

Although chest radiographic and chest computed-tomographic imaging were used to diagnose COVID-19, it appears that chest computed tomographic imaging and chest radiograph findings in 15% of40% of patients, respectively, might be normal in the early phase of the disease [21].

Treatment involves managing acute hypoxic respiratory failure and ARDS; evidence-based guidelines have been established by several countries and experts, including those updated regularly by the National Institutes of Health (NIH) [40]. It appears that over 75% of individuals with COVID-19 admitted to the hospital need supplemental oxygen through a nasal cannula, simple facemask, or non-rebreather mask; for those unresponsive to conventional oxygen therapy, heated high-flow nasal cannula oxygen may be given [40]**.**

Dexamethasone improves survival in hospitalized patients who require supplemental oxygen, with high efficacy observed in patients who demand mechanical ventilation, and its usage is highly suggested here [41, 42]. A large clinical trial proved that dexamethasone decreases mortality by about one-third in critically ill patients [43].

Antiviral Agents such as lopinavir/ritonavir (400/100 mg po, every 12 hours) are recommended [44]. However, a randomized, open-label trial revealed no advantage for using lopinavir/ritonavir compared to standard care [45]. Favipiravir (Anti-flu medication) appears to be effective against SARS-CoV-2 in vitro. Arbidol (broad-spectrum antiviral) could increase the discharg rate and reduce the mortality rate, as demonstrated in a retrospective study [46].

Thromboprophylaxis administration is recommended for patients with COVID-19 as they have a high incidence of venous thromboembolism, and the anticoagulant treatment was related to decreased ICU mortality. Additionally, full therapeutic-intensity anticoagulation is indicated in the case of known thrombophilia or thrombosis [47].

Tocilizumab (a monoclonal antibody directed against the IL-6 receptors) was used in addition to standard therapies in Italy. Phase two and three clinical trials on sarilumab (anti-IL-6 receptor antibody) are ongoing in the USA [47]. Anakinra (recombinant IL-1 receptor antagonist) was also used [48].

Targeting excessive host inflammation can achieved using Acalabrutinib (a Bruton tyrosine kinase inhibitor), that regulate macrophage signaling and triggering. [49] Bamlanivimab, casirivimab, and imdevimab are monoclonal antibodies available for outpatients at high risk under Emergency Use Authorizations [50].

When secondary bacterial infection is suspected, antibiotics should be used. However, inappropriate usage should be avoided, despite recommendations [51].

In 2016, Remdesivir (RDV) revealed in vitro activity against Marburg virus, Ebola virus, Pneumoviridae (such as a respiratory syncytial virus), and Paramyxoviridae (such as Nipah virus, parainfluenza type 3 virus, measles, and mumps viruses, and Hendra virus) [52]. On October 22, 2020, the antiviral drug RDV (Veklury—Gilead Sciences) was authorized by the FDA as the first therapy for adults and pediatrics patients older than 12 years and at least 40 kg (about 88 lb) who have been hospitalized with severe COVID-19 [53].

Remdesivir is an adenosine analog prodrug that possesses an antiviral effect against many RNA viruses [54]. RDV revealed in vitro and in vivo activity against SARS-CoV-2 [55].

Patients who likely benefit from RDV are in the early stage of COVID-19 with a high possibility of developing to the critical stage [56]. RDV is unsuitable for adults and adolescents whose eGFR is < 30 mL/min or are on renal replacement treatment and is used with caution for those with an eGFR of 30 – 50 mL/min. It should also be avoided in pregnancy unless the benefit outweighs the risks [57, 58].

Remdesivir is administered as a single loading dose of 200mg intravenously on day 1, followed by a maintenance dose of Remdesivir 100 mg/ once daily up to 10 days. Remdesivir is administered via intravenous infusion in a total volume of 250 ml 0.9% sodium chloride over 30 to 120 minutes [56]. Monitoring of renal and liver function during treatment with Remdesivir is recommended. The main side effects are nausea, diarrhea or constipation, elevated liver enzymes, kidney injury, dysfunction, multiple organ dysfunction syndromes, and deep vein thrombosis [59].

The current study intended to compare the effect of timing of Remdesivir administration on the duration of hospitalization and clinical outcome of hospitalized patients with severe COVID-19 in Imam Al-Hussain medical city, those who received Remdesivir early; in the first week, with others who received it in the second week of the symptom's onset.

Patients and Methods

Study design and setting

A retrospective comparative study was conducted in Imam Al-Hussain medical city from October 1 to November 30 of 2020. Data were collected from the patient's registry database to explore those with a laboratory-confirmed or radiological diagnosis of COVID-19 for whom observed at Imam Al-Hussain medical city. COVID-19 cases were confirmed depending on the positive result of high-throughput sequencing or real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assays or positive radiological findings alongside the clinical symptoms following the WHO guidelines.

Inclusion criteria

Consist of all patients hospitalized for severe COVID-19 and have received 5 to 10 doses of RDV within the first two weeks of symptoms onset. All patients received dexamethasone and a prophylactic dose of enoxaparin while receiving RDV.

Exclusion criteria

Patients with a mild, moderate, and critical illness, patients who received RDV after 14 days of symptoms onset, patients had been received less than 4 doses of RDV, patients on mechanical ventilation, and those with eGFR < 30 ml/min, or ALT, AST more than 5 times the upper normal limit.

Data Collection

The data was collected from the records of two groups of patients with severe COVID-19 (those

who received RDV in the first week of symptoms and those who received it in the second week of symptoms), then comparison was made between the two groups regarding the clinical outcome, lab results, duration of recovery and death.

Ethical consideration

Approval of the study protocol was obtained from the scientific committee of internal medicine in the Iraqi board committee in Baghdad.

Statistical analysis

After collecting the data, responses were checked for incompletely filled questionnaires. The Statistical Package for the Social Sciences (SPSS version 23) was used to analyze the data.

Results

The association between the timing of RDV administration and the clinical outcome

95.6% of the patients received RDV in the first week of the onset of the symptoms improved, and 4.4% died while 84.5 % of the patients received RDV in the second week of the symptoms improved, and 15.5% died

There is a statistically significant association between the timing of RDV administration and the clinical outcome of the patients with severe COVID-19 with a P-value of (0.046), (Table 1). In patients who received RDV during the first week of the symptoms, 63.1% were improved within a week, 26.2% showed improvement within 7-11 days, and the remaining (10.8%) improved in more than11 days. In contrast, patients who received RDV in the second week of the onset of the symptoms, 46.7% of them improved in less than7 days, 15% improved within 7-11, and the remaining (38.3%) improved in more than 11 days, (Table 2).

Table 1. shows the association between the timing of RDV administration and the clinical outcome in patients with severe COVID-19.

			Timing of RDV administration		
			1st week	2nd week	Total
clinical outcome	**Improved**	Count	65	60	125
		% within Timing of administration	95.6%	84.5%	
		% of Total	46.8%	43.2%	89.9%
	Dead	Count	3	11	14
		% within Timing of administration	4.4%	15.5%	
		% of Total	2.2%	7.9%	10.1%
Total		Count	68	71	139
***p –value 0.046**		% of Total	48.9%	51.1%	100.0%

*Chi- square test

Table 2. Shows the association between timing of RDV administration and time of recovery with the clinical outcome.

Timing of Remdesivir administration			Duration of recovery(days)			
			< 7	7-11	>11	Total
***P-value 0.001**	**1st week**	Count	41	17	7	65
		% within Timing of Remdesivir administration	63.1%	26.2%	10.8%	100.0%
		% of Total	32.8%	13.6%	5.6%	52.0%
	2nd week	Count	28	9	23	60
		% within Timing of Remdesivir administration	46.7%	15.0%	38.3%	100.0%
		% of Total	22.4%	7.2%	18.4%	48.0%
	Total	Count	69	26	30	125
		% of Total	55.2%	20.8%	24.0%	100.0%

*Chi- square test

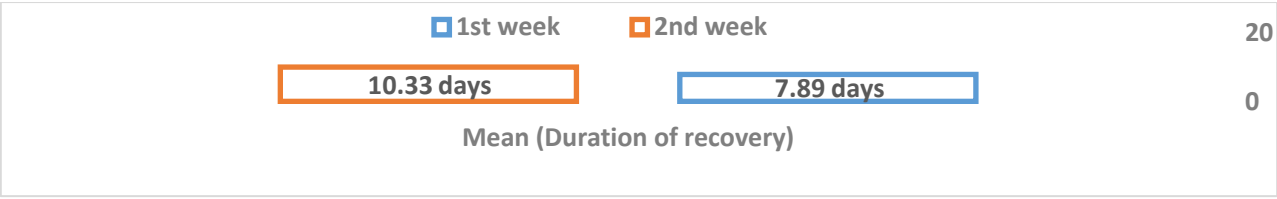

Figure 1. Means of the recovery time for patients according to the timing of Remdesivir administration.

Discussion

This study retrospectively describes the clinical outcomes and recovery duration of patients with confirmed Covid-19 infection who were severely ill and treated with RDV. Improvement in oxygen-support status was more in patients who received RDV in the first week than those who received it in the second week. These results agreed with a Goldman study that found the discharge rates were higher (62% versus 49%) in patients receiving the first dose of Remdesivir within ten days of symptoms onset compared to those who received the first dose after ten or more days [(5)]. This study result is inconsistent with the Adaptive Covid-19 Treatment Trial (ACTT-1) international RCT, which found no difference in the effect of RDV when comparing initiation before or after 10 days from symptom onset [(6)].

In this study, RDV administration in the first week of symptoms was superior to administration in the second week regarding recovery duration, which is shorter for patients in the first group (median 6 days) than the second group (median 8.5 days), which means approximately 2 days reduction in the recovery duration. This agrees with the first published double-blind placebo-controlled randomized controlled trial (RCT) investigating the use of Remdesivir in COVID-19, which was a multicenter study in China; Interestingly When Remdesivir was administered within ten days of symptom onset, a five-day reduction in time to clinical improvement was achieved, in contrast to a one-day reduction if administered later than ten days [(7)]. In addition, Remdesivir was better than the control in reducing the time to recovery in patients hospitalized with Covid-19 and had evidence of lower respiratory tract infection [(6).] The comparative analysis demonstrated greater clinical recovery and lower mortality in hospitalized patients receiving RDV (Gilead SIMPLE 5773 study) compared to a matched cohort receiving standard of care (Gilead 5807 study) [(8)].

In contrast to Wang et al.'s findings, this study revealed a statistically significant relationship between the timing of RDV administration and recovery duration with the P-value of (0.002) [(7)]. Also, the case fatality rate was lower in those who received RDV early (2.2%) than those who received it late (7.9%).

The median interval between RDV initiation and death for patients who received it early was 17 days (range 4 to 18 days), while the median interval for patients who received it late was ten days (range 5 to 17 days). These findings agree with Grein's study [(9)], which found that the median interval between RDV initiation and death was 15 days, and Beigel's study, in which at 14-day the mortality rate was lower in the Remdesivir group; however, no statistically significant difference was obtained. Also, the 28-day mortality rate was not available at publication [(6)]. Inconsistent with Wang et al.'s trial [(7)], the WHO's Solidarity trial, compared with standard care, RDV did not reduce in-hospital 28-day mortality, either overall or in any subgroup [(10)].

Conclusions

This comparative study results suggest that recovery duration is associated significantly with the time of RDV administration. The recovery time was shorter for patients receiving Remdesivir in the first week than patients who received Remdesivir in the second week of the onset of symptoms. The case fatality rate in patients who received RDV in the first week of the symptom onset was lower than the case fatality rate in patients who received RDV in the second week in severe COVID-19 infection. However, a randomized clinical trial is required to conclude the effectiveness of RDV. It will also be important to test the drug on this scale to ensure safety in COVID19 patients.

Limitations of the Study

This study is a retrospective study so that the probability of the presence of missing data increases. Also, some patients might be discharged before completing the investigation needed for the study.

Other therapeutic strategies that have been used show clinical benefit in COVID-19. Mostly, use of dexamethasone reduced mortality in severe COVID-19, **which** may interfere with the effect of RDV.

The current study did not collect viral load data to confirm the antiviral effects of Remdesivir or any association between baseline viral load and viral suppression if any, and clinical response.

Conflicts of interest

The author confirms that this paper's content has no conflict of interest.

Financing

The author received no funds from any source to cover the expenses of this study.

References

1. Young CAJPT. Remdesivir gains FDA approval as first treatment for COVID-19.27(1):16-7.
2. Pizzorno A, Padey B, Julien T, Trouillet-Assant S, Traversier A, Errazuriz-Cerda E, et al. Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia. 2020.

3. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020;117(12):6771-6.
4. Health NIo. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Available from: https://www.covid19treatmentguidelines.nih.gov].
5. Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. 2020;383(19):1827-37.
6. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. 2020;383(19):1813-26.
7. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. 2020;395(10236):1569-78.
8. Olender SA, Perez KK, Go AS, Balani B, Price-Haywood EG, Shah NS, et al. Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care. Clinical Infectious Diseases. 2020.
9. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. 2020;382(24):2327-36.
10. Medicine WSTCJNEJo. Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. 2021;384(6):497-511.
11. Organization WH. WHO coronavirus disease (COVID-19) Dashboard. Data last updated: 2020//11. 2020.
12. Riou J, Althaus CLJE. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. 2020;25(4):2000058.
13. Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. 2020;9(1):386-9.
14. Chen W, Lan Y, Yuan X, Deng X, Li Y, Cai X, et al. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. 2020;9(1):469-73.
15. Li C, Zhao C, Bao J, Tang B, Wang Y, Gu BJCCA, et al. Laboratory diagnosis of coronavirus disease-2019 (COVID-19). 2020;510:35.
16. Control CfD, Prevention. Coronavirus Disease 2019–How It Spreads. 2020.
17. Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. 2020;323(14):1406-7.
18. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. 2020.
19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. 2020;395(10223):497-506.
20. Kun-Ling S, Yong-Hong YJhlsccps---p. Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. 2020.
21. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. 2020;382(18):1708-20.
22. Song Y, Liu P, Shi X, Chu Y, Zhang J, Xia J, et al. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. 2020;69(6):1143-4.
23. Shi M, Chen L, Yang Y, Zhang J, Xu J, Xu G, et al. Analysis of clinical features and outcomes of 161 patients with severe and critical COVID-19: A multicenter descriptive study. 2020;34(9):e23415.
24. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney international. 2020;97(5):829-38.
25. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. The Lancet Respiratory medicine. 2020;8(7):738-42.
26. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054-62.
27. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. 2020;26(7):1017-32.
28. Shimizu M. Clinical features of cytokine storm syndrome. Cytokine storm syndrome: Springer; 2019. p. 31-41.
29. Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-RJIjoaa. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. 2020;55(3):105924.
30. Ruan Q, Yang K, Wang W, Jiang L, Song JJIcm. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. 2020;46(5):846-8.
31. Cheng MP, Papenburg J, Desjardins M, Kanjilal S, Quach C, Libman M, et al. Diagnostic testing for severe acute respiratory syndrome–related coronavirus 2: a narrative review. 2020;172(11):726-34.
32. Binnicker MJJCc. Emergence of a novel coronavirus disease (COVID-19) and the importance of diagnostic testing: why partnership between clinical laboratories, public health agencies, and industry is essential to control the outbreak. 2020;66(5):664-6.
33. Tsang NNY, So HC, Ng KY, Cowling BJ, Leung GM, Ip DKMJTLID. Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. 2021.
34. Sheridan CJNB. Fast, portable tests come online to curb coronavirus pandemic. 2020;38(5):515-8.
35. Prendergast C, Papenburg JJFm. Rapid antigen-based testing for respiratory syncytial virus: moving diagnostics from bench to bedside? 2013;8(4):435-44.
36. Berger A, Nsoga MTN, Perez-Rodriguez FJ, Aad YA, Sattonnet-Roche P, Gayet-Ageron A, et al. Diagnostic accuracy of two commercial SARS-CoV-2 Antigen-detecting rapid tests at the point of care in community-based testing centers. 2021;16(3):e0248921.
37. Sethuraman N, Jeremiah SS, Ryo AJJ. Interpreting diagnostic tests for SARS-CoV-2. 2020;323(22):2249-51.
38. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). 2020;71(15):778-85.

39. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky AJLs. The role of biomarkers in diagnosis of COVID-19–A systematic review. 2020:117788.
40. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). 2020;46(5):854-87.
41. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. 2020.
42. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. 2020;324(13):1307-16.
43. Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. Nature. 2020;582(7813):469.
44. Bimonte S, Crispo A, Amore A, Celentano E, Cuomo A, Cascella M. Potential Antiviral Drugs for SARS-Cov-2 Treatment: Preclinical Findings and Ongoing Clinical Research. In vivo (Athens, Greece). 2020;34(3 Suppl):1597-602.
45. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382(19):1787-99.
46. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(15):769-77.
47. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. The Lancet Rheumatology. 2020;2(6):e325-e31.
48. Roschewski M, Lionakis MS, Sharman JP, Roswarski J, Goy A, Monticelli MA, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. Science immunology. 2020;5(48).
49. Kucharski AJ, Klepac P, Conlan AJK, Kissler SM, Tang ML, Fry H, et al. Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study. The Lancet Infectious diseases. 2020;20(10):1151-60.
50. COVID-19 Treatment Guidelines Panel.Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [Internet]. 2020.
51. Liu C, Wen Y, Wan W, Lei J, Jiang XJIi. Clinical characteristics and antibiotics treatment in suspected bacterial infection patients with COVID-19. 2021;90:107157.
52. Esposito S, Noviello S, Pagliano PJIM. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. 2020;28(2):198-211.
53. Young CAJPT. Remdesivir gains FDA approval as first treatment for COVID-19.27(1):16-7.
54. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020;117(12):6771-6.
55. Pizzorno A, Padey B, Julien T, Trouillet-Assant S, Traversier A, Errazuriz-Cerda E, et al. Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia. 2020.
56. Health NIo. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Available from: https://www.covid19treatmentguidelines.nih.gov.
57. Docherty AB, Harrison EM, Green CA, Hardwick H, Pius R, Norman L, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv. 2020:2020.04.23.20076042.
58. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. 2020;382(17):1663-5.
59. Charan J, Kaur RJ, Bhardwaj P, Haque M, Sharma P, Misra S, et al. Rapid review of suspected adverse drug events due to remdesivir in the WHO database; findings and implications. 2021;14(1):95-103.