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Original Article

TREATMENT PROFILE AND SURVIVAL ANALYSIS *ACUTE RESPIRATORY DISTRESS SYNDROME* (ARDS) COVID-19 PATIENTS

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ABSTRACT

Objective of the review was to evaluate the correlation between treatment profile and survival analysis among *Acute Respiratory Distress Syndrome* (ARDS) covid-19 patients. Journals were searched from Google scholar, Elsevier and Pubmed with references from 2018 to 2021. Hydroxychloroquine and favipiravir has a good outcome in treating severe to critical illness patients. Ivermectin has a better output on treating mild to moderate symptoms covid-19 but further study is required to know the outcome from treating severe to critical illness. Oseltamivir only works on mild cases of covid-19, early-onset therapy on patient covid-19 can reduce the time of fever. An antibacterial is applied on the covid-19 patients with pneumonia and for cytokine storm patients required tocilizumab on therapy. Severe to critical cases of covid-19 can be given corticosteroid. Lopinavir/ritonavir and ribavirin have a poor antiviral activity against SARS-CoV-2. In conclusion, **f**or severe to critical illness required hydroxychloroquine or favipiravir as antiviral agent plus antibacterial agent, if cytokine storm is developed tocilizumab can be given. For mild to moderate symptoms can be given oseltamivir or ivermectin, if there is a sign of bacterial infection (pneumonia) an antibacterial agent can be given.

Keywords: Covid-19, treatment, Survival rate, Antiviral, Antibacterial

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that caused disease that know as COVID-19 [1]. This virus is confirmed for the first time in the end of 2019 at Wuhan China by the zoonotic caused [2]. Until December 22nd (12.56 GMT+7) there are more than 276 million cases had been confirmed with the total people dead more than 5 million. SARS-CoV-2 is an infection that may cause lung inflammation and *acute respiratory distress syndrome* (ARDS) [3]. Fever, cough, myalgia, fatigue and shortness of breath are the most common symptoms covid-19 that had been reported [4].

There are 3 categories of severity COVID-19 according to the WHO: [1] Critical COVID-19 [*Acute Respiratory Distress Syndrome* (ARDS), sepsis, septic shock or patient required life sustaining therapy] [2] Severe COVID-19 [SpO_2<90%, have signs of ARDS and pneumonia] and [3] Non-Severe COVID-19 [absence of criteria for severe or critical signs] [5].

According to the Health Minister of Republic of Indonesia there are 4 categories of severity COVID-19: [1] asymptomatic, [2] moderate symptoms [patient with pneumonia symptoms and SpO_2 93–95 %], [3] severe symptoms [patient with pneumonia and SpO_2<93%] and [4] critical illness [patient with *Acute Respiratory Distress Syndrome* (ARDS), sepsis and septic shock] [6].

For the critical illness with ARDS (*Acute Respiratory Distress Symptoms*) there 4 categories: [1] mild ARDS [200 mmHg<PaO_2/FiO_2 ≤ 300 mmHg (PEEP or CPAP ≥ 5 cmH_2O, or without using ventilator)], [2] moderate ARDS [100<PaO_2/FiO_2 ≤ 200 mmHg (PEEP ≥ 5 cmH_2O, or without using ventilator)], [3] severe ARDS [PaO_2/FiO_2 ≤ 100 mmHg (PEEP ≥ 5 cm H_2O, or without using ventilator)] and [4] critical ARDS [when PaO_2 cannot be found without using ventilator but SpO_2/FiO_2 ≤ 315 can be marker] [7].

MATERIALS AND METHODS

Searching the articles associated with the treatment and survival rate of covid-19 patients. Inclusion criteria were the article that have a treatment and survival and the exclusion is the articles that had only treatment profile or survival rate. There are 83 journals but only 12 journals that fulfill the criteria.

RESULTS AND DISCUSSION

A derivate chloroquine antimalaria drug, hydroxychloroquine, has been reported that had an antiviral activity at *in vivo* trial [8, 9]. In a study that a different survival rate that use hydroxychloroquine (n = 4542) and without use hydroxychloroquine (n = 3533) show a significant correlation of survival rate (P<0.0001) [10]. Comorbidities that have a significant correlation are cardiovascular disease (P<0.0001), arterial hypertension (P = 0.0002), chronic renal disease (P<0.0001), neurological disorders (P<0.0001), Cognitive disorder (P<0.0001) and immunosuppressive (P = 0.0006). The use of hydroxychloroquine can decrease mortality of the patients. The secretion of tumor necrosis factor α (TNFα) that caused cytokine storm can be reduced by applying hydroxychloroquine [11].

An IL-6 receptor antagonist, tocilizumab can inhibit cytokine storm by blocking the IL-6 signal transduction pathway [12]. Rapid virus multiplication with extensive inflammatory cell infiltration and enhanced pro-inflammatory cytokine responses have been documented with pathogenic SARS-CoV-2 [13]. A study from price *et al.* shows that the used of tocilizumab has a significant correlation (P = 0.02) with a survival rate 85% (130 out of 153 patients) [14]. A study shows 15 from 20 (85%) oxygen intake had been lowered by the patients after 5 d using tocilizumab and 1 patient did not need the oxygen therapy [15].

A combination of antiviral drug single dose or with chloroquine and hydroxychloroquine; the combination of favipiravir with chloroquine and oseltamivir+chloroquine has a significant correlation between drug and survival rate (P = 0.025) [16]. From another study shows that combination azithromycin with/without hydroxychloroquine have a significant favorable outcome (P = 0.04) than patients without treatment, the patient who benefits on azithromycin with/without hydroxychloroquine with lymphocyte count ≥ 1000/mm^3(P = 0.004) and C-Reactive Protein ≥ 100 mg/dl (P = 0.009) have a disadvantageous outcome; beside that, the oxygen flow needs had shown a significant correlation with the unfavorable outcome/death/admission to ICU (P<0.001) [17]. The use of oseltamivir in the early treatment (31+/-21 h) have a significant correlation between late treatment (94+/-38 h) on duration of fever (P<0.001) [18]. In adults hospitalized with moderate to severe covid-19 pneumonia study had been found that there is no significant correlation on clinical outcome between favipiravir plus inhaled interferon beta-1b and hydroxychloroquine (P = 0,778) [19].

According tong *et al.* study show there is ribavirin cannot decrease the mortality of covid-19 (P = 0.475), result between the control group and ribavirin in the immunoglobulin therapy (P = 0.143), non-

invasive ventilation support (P = 0.750), Invasive ventilation support (P = 0,302) and corticosteroid therapy (P = 0,288) need are unsignificant [20].

A study of apply corticosteroid on patients covid-19 shows use of corticosteroid can reduce used of lopinavir (P<0.0001) and/or hydroxychloroquine (P = 0,049) but increase the needs of oxygen therapy (P = 0.01) and unsignificant survival rate of use corticosteroid has found (P = 0.70) [21]. Because of the lack evidence of corticosteroid on covid-19 WHO recommended the use corticosteroid only apply on patient with severe and critical symptoms. A systemic corticosteroid is highly recommended rather than no systemic corticosteroid [22]. The used of dexamethasone 6 mg for more 10 d decreases 28 d mortality covid-19 patients who receiving respiratory support [23].

Ivermectin has shown an antiviral agent against HIV, dengue, influenza and SARS-CoV-2 in *in vitro* studies [24]. Ivermectin-doxycycline (group A) in this test show a high percentage recovery rate (100%) and faster recovery duration (8.93 d) than hydroxychloroquine-azithromycin (group B) (96.36%, 9.33 d), even though there are no statistically significant correlation between treatment group A and group B; this study only includes the patients with mild to moderate symptoms of covid-19 [25]. According to Babalola *et al.*, a significant correlation duration of treatment between ivermectin 6 mg (6 d+/-2.95), ivermectin 12 mg (4.65 d+/-3.19) twice weekly for two weeks and lopinavir/ritonavir (9.15+/-7.26) daily for two weeks have been found (p = 0.02), but an increase of the arterial oxygen saturation (SpO_2%) was associated by the ivermectin treatment even though there is no significant correlation (P = 0.073), the increase of platelets (P = 0.005) with the significant correlation has been found [26].

According to Cao *et al.* study, lopinavir-ritonavir has no benefit that involving covid-19 patient with severe symptoms, the result shows there is no statistically significant but the patient who received lopinavir-ritonavir had shorter stay at intensive care unit (ICU) for 5 d [27]. A study shows that arbidol an antiviral drug has more evidence than lopinavir/ritonavir, the applying arbidol monotherapy on covid-19 patients show a significant correlation between duration of treatment (P<0.01) with lopinavir/ritonavir (11.5 d) and arbidol monotherapy (9.5 d) [28].

In ramatillah *et al.* study shows a significant correlation between the treatment given to the patient has comorbidity and without comorbidity (P<0.0001) and either of duration treatment of the patient has a significant correlation (P<0.0001) [29].

Table 1: List of drug

Drug name	Indication	Appropriate	Monitoring
Hydroxychloroquine	Antiviral, inhibitor TNFα	Yes, because hydroxychloroquine has a good clinical treatment to cure covid-19 in single dose or combination drug and less toxicity than chloroquine	Cardiovascular (prolonged QT interval 93%)
Chloroquine	Antiviral	Yes, but hydroxychloroquine the one of chloroquine derivate is more prefer because of the less toxicity	Cardiovascular (cardiomyopathy, prolonged QT interval)
Lopinavir/ritonavir	Antiviral	No, because lopinavir/ritonavir has low antiviral activity against covid1-19	Gastrointestinal tract such as diarhea [30]
Oseltamivir	Antiviral	Yes, only working on mild case of covid-19 use in the early treatment to decrease the symptoms to develop	-
Favipiravir	Antiviral	Yes, working well on covid-19 patient with moderate symptoms	gastrointestinal, teratogenicity and QTc Prolongation
Ribavirin	Antiviral	No, have less antiviral activity against covid-19	-
Tocilizumab	IL-6 receptor antagonist	Yes, use with combination antiviral and antibiotic on cytokine storm patient or *Acute Respiratory Distress Syndrome* (ARDS) patient	Gastrointestinal (constipation, diarrhea and nausea), ALT/SPGT level
Corticosteroid (dexamethasone 6 mg)	Corticosteroid	Yes, only use for patient with severe to critical illness of SARS-CoV-2 infection	SpO_2 or oxygen need
Ivermectin	Anti-parasitic, antiviral	Yes, use with or without combination antibiotic but still need more evidence to use on severe to critical illness patient	SpO_2 and platelets count
Azithromycin	Antibacterial	Yes, use along with antiviral agents on covid-19 patient with pneumonia	Prolonged QT interval
Arbidol	Antiviral	Yes, but still need a further study about this drug in treat covid-19	-
Doxycycline	Antibacterial	Yes, use along antiviral/ivermectin because a good clinical outcome on covid-19 patient with pneumonia	-
Ceftriaxone	Antibacterial	Yes, use along antiviral agent on covid-19 patient with pneumonia	-

CONCLUSION

The severity covid-19 had an impact in choosing drug therapy. The patient which has a severity to critical illness can be treat by favipiravir or hydroxychloroquine plus antibacterial agent (azithromycin) plus corticosteroid, if the patient develop cytokine storm, an IL-6 receptor antagonist (tocilizumab) can be given on therapy. For a patient has a mild to moderate symptoms, oseltamivir or ivermectin can be given as therapy but if the patient develops a bacterial infection an antibacterial can be given.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declare none

REFERENCES

1. Sunggoro AJ, Purwanto I, Hasan M. Trombosis pada corona virus disease (COVID-19). J Kedokteran Syiah Kuala. 2020 Dec 1;20(3). doi: 10.24815/jks.v20i3.18689.
2. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91-8. doi: 10.1016/j.jare.2020.03.005, PMID 32257431.
3. Correale P, Caracciolo M, Bilotta F, Conte M, Cuzzola M, Falcone C, Mangano C, Falzea AC, Iuliano E, Morabito A, Foti G, Armentano A, Caraglia M, De Lorenzo A, Sitkovsky M, Macheda S. Therapeutic effects of adenosine in high flow 21% oxygen aereosol in patients with Covid19-pneumonia. PLOS ONE. 2020 Oct 1;15(10):e0239692. doi: 10.1371/journal.pone.0239692, PMID 33031409.
4. Gee S, Gaughran F, MacCabe J, Shergill S, Whiskey E, Taylor D. Management of clozapine treatment during the COVID-19 pandemic. Ther Adv Psychopharmacol. 2020 Jan;10:2045125320928167. doi: 10.1177/2045125320928167, PMID 32542111.

5. Health Organization W. Guideline Therapeutics and COVID-19: living guideline; 2021.
6. Menteri K. Kesehatan republik indonesia. Available from: https://covid19.go.id/storage/app/media/Regulasi/2021/Agustus/kmk-no-hk0107-menkes-5671-2021-ttg-manajemen-klinis-tata-laksana-covid-19-di-fasilitas-pelayanan-kesehatan-signed-1.pdf. [Last accessed on 13 Dec 2021].
7. WHO-2019-nCoV-clinical-2020.4-chi. Available from: https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-chi.pdf. [Last accessed on 13 Dec 2021]
8. Keyaerts E, Vijgen L, Maes P, Neyts J, van Ranst M. *In vitro* inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004 Oct 8;323(1):264-8. doi: 10.1016/j.bbrc.2004.08.085, PMID 15351731.
9. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, Seidah NG, Nichol ST. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005 Aug 22;2:69. doi: 10.1186/1743-422X-2-69, PMID 16115318.
10. Catteau L, Dauby N, Montourcy M, Bottieau E, Hautekiet J, Goetghebeur E, van Ierssel S, Duysburgh E, Van Oyen H, Wyndham Thomas C, Van Beckhoven D, Belgian Collaborative Group on COVID-19 Hospital Surveillance. Low-dose hydroxychloroquine therapy and mortality in hospitalized patients with COVID-19: a nationwide observational study of 8075 participants. Int J Antimicrob Agents. 2020 Oct 1;56(4):106144. doi: 10.1016/j.ijantimicag.2020.106144, PMID 32853673.
11. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003 Nov;3(11):722-7. doi: 10.1016/s1473-3099(03)00806-5, PMID 14592603.
12. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021;93(1):250-6. doi: 10.1002/jmv.26232, PMID 32592501.
13. Mehta Y, Dixit SB, Zirpe KG, Ansari AS. Cytokine storm in novel coronavirus disease (COVID-19): Expert management considerations. Vol. 24. Indian Journal of Critical Care Medicine. Jaypee Brothers Medical Publishers (P) Ltd; 2020. p. 429–34.
14. Price CC, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G, Azar MM, Mcmanus D, Chen SC, Gleeson SE, Britto CJ, Azmy V, Kaman K, Gaston DC, Davis M, Burrello T, Harris Z, Villanueva MS, Aoun-Barakat L, Kang I, Seropian S, Chupp G, Bucala R, Kaminski N, Lee AI, LoRusso PM, Topal JE, Dela Cruz C, Malinis M. Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus Disease 2019: survival and clinical outcomes. Chest. 2020 Oct 1;158(4):1397-408. doi: 10.1016/j.chest.2020.06.006, PMID 32553536.
15. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020 May 19;117(20):10970-5. doi: 10.1073/pnas.2005615117, PMID 32350134.
16. Ramatillah DL, Isnaini S. Treatment profiles and clinical outcomes of COVID-19 patients at a private hospital in Jakarta. PLOS ONE. 2021 Apr 1;16(4) (Apr 4):e0250147. doi: 10.1371/journal.pone.0250147, PMID 33861777.
17. Davido B, Boussaid G, Vaugier I, Lansaman T, Bouchand F, Lawrence C, Alvarez JC, Moine P, Perronne V, Barbot F, Saleh Mghir A, Perronne C, Annane D, De Truchis P, COVID-19 RPC Team. Impact of medical care, including use of anti-infective agents, on prognosis of COVID-19 hospitalized patients over time. Int J Antimicrob Agents. 2020 Oct 1;56(4):106129. doi: 10.1016/j.ijantimicag.2020.106129, PMID 32755653.
18. Chiba S. Effect of early oseltamivir on outpatients without hypoxia with suspected COVID-19. Wien Klin Wochenschr. 2021 Apr 1;133(7-8):292-7. doi: 10.1007/s00508-020-01780-0, PMID 33296027.
19. Khamis F, Al Naabi H, Al Lawati A, Ambusaidi Z, Al Sharji M, Al Barwani U, Pandak N, Al Balushi Z, Al Bahrani M, Al Salmi I, Al-Zakwani I. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. Int J Infect Dis. 2021 Jan 1;102:538-43. doi: 10.1016/j.ijid.2020.11.008, PMID 33181328.
20. Tong S, Su Y, Yu Y, Wu C, Chen J, Wang S, Jiang J. Ribavirin therapy for severe COVID-19: a retrospective cohort study. Int J Antimicrob Agents. 2020 Sep 1;56(3):106114. doi: 10.1016/j.ijantimicag.2020.106114, PMID 32712334.
21. Bani Sadr F, Hentzien M, Pascard M, N'Guyen Y, Servettaz A, Andreoletti L, Kanagaratnam L, Jolly D. Corticosteroid therapy for patients with COVID-19 pneumonia: a before-after study. Int J Antimicrob Agents. 2020 Aug 1;56(2):106077. doi: 10.1016/j.ijantimicag.2020.106077, PMID 32634602.
22. Corticosteroids for COVID-19; 2020. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. [Last accessed on 22 Dec 2021]
23. Dexamethasone in hospitalized patients with covid-19. N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436.
24. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res. 2020 Jun 1;178:104787. doi: 10.1016/j.antiviral.2020.104787, PMID 32251768.
25. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients; 2020.
26. Title EB O. Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double blind dose-response study in Lagos. doi: 10.1101/2021.01.05.21249131.
27. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020 May 7;382(19):1787-99. doi: 10.1056/NEJMoa2001282, PMID 32187464.
28. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, Lu J, Xue Y. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020 Jul 1;81(1):e21-3. doi: 10.1016/j.jinf.2020.03.060, PMID 32283143.
29. Ramatillah DL, Gan SH, Sulaiman SAS, Puja D, Abubakar U, Jaber AAS, Lukas S, Jusnita N. Evaluation of treatment outcome for pneumonia among pre-vaccinated COVID-19 Patients with/without comorbidity in a Public Hospital in Bengkulu, Indonesia. Vaccines (Basel). 2021;9(12). doi: 10.3390/vaccines9121411, PMID 34960157.
30. Clinical efficacy of lopinavir/ritonavir in the treatment of coronavirus disease 2019 [internet]. p. uniroma1. Italianist. Available from: https://web/spec_medint/sites/default/files/3390-3396.pdf. [Last accessed on 23 Dec 2021].