COVID-19 in Indonesia: Where Are We?

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In-country that has 265 million population[1] and carrying a double burden due to changing pattern of morbidity, mortality and disability[2], a prompt and effective disease control should be unarguable. By 3.5 months since the 1st case officially confirmed, Indonesia recorded more than 1000 new cases daily. The national trend shows no sign of decrease as 19 September 2020 the report sets a new mark of 4000 new cases in a day.[3] Earlier this month, President Jokowi affirms the national fatality (of detected positive cases) is above the global average.[4] Matching to decentralized governance, reported transmissions and responses on controlling it is observed varied across the regions.

The concept of controlling disease transmission relies on contacts suppression; and on the longer end, relies on vaccinations. As 27 September 2020, no vaccine is approved for use in the general population. Until then, countries should implement early, widespread, and strict disease mitigation strategies. While much remains to be learned on COVID-19, global evidence assert at least three strategies at the population level contributes to flatten the curve: mobility restriction, testing and isolation and rigorous contact-tracing.[5-9] At the individual level, strict compliance on practising preventive behaviours: physical distancing, mask-wearing and proper handwashing, could reduce risk of infection.[8,10] While many are struggling, some countries that have achieved low incidence of COVID-19 exhibit exemplary disease surveillance and health information system. Here in Indonesia, both are works in progress; challenging the much-needed evidence-based actions. As such, how exactly Indonesia works on suppressing this unprecedented pandemic gain us costly lessons learned.

Notably, the health information system must be strengthened to record disease discourse from contact to an outcome. Reliable, quality and timely information system are unquestionably pivotal. This might sound obvious, but the fact that many COVID-19 are asymptomatic[11] and some would develop symptoms on the estimate of 2-14 days12 makes a substantial number of transmissions could go undetected; especially for countries that test only the symptomatic. Some epidemiologists suggest Indonesia does not yet have an epidemic curve, and the notion might not be baseless. Analysis of COVID-19 data shows testing delay between three to seven days13 implying report of positive cases is not a timely reflection of actual disease transmission on the field. For Indonesia that is constrained by its limited testing capacity, delays or mistakes in disease control would be devastating, if not, catastrophic.

Indonesia is not on entire absences of actions, but the epidemic calls for more. The central government called for social distancing two weeks after the first case confirmed and regulation on the large scale social distancing (*Pembatasan Sosial Berskala Besar*/ PSBB) that restrict non-essential population mobility is enacted by April 2020. The provincial government can declare PSBB upon central government approval. The capital, DKI Jakarta, was first to act on school and business closures

on mid-March then went full PSBB on 10 April 2020. Such mobility restrictions were found effective on suppressing transmission, the COVID-19 effective reproduction number (Rt) decreased from 2.0 in April 2020 to 1.2 in June 2020 when at least half population complying to staying at home.[13-15] The Rt steadily increased by June 2020 when it's relaxed.[13] Understandably, mobility restriction is not feasible for the long run, but Wuhan showcased an uncontrolled epidemic is damaging and traumatic for personnel, community and system. Acknowledging strict and long term PSBB is no longer a viable option, Indonesia must outpace the transmission with other interventions.

As mentioned, suppressing COVID-19 transmissions demands population involvement to comply and be discipline on proven effective preventive behaviours: physical distancing, proper mask-wearing and handwashing with soap.[8,10] To our knowledge, there is no systematic measurement of preventive measures coverages in the population. Some telephone-based and online surveys reported high coverage of face mask use. Nevertheless, direct interview of preventive measures tends to have social desirability bias.[16] Our model indicates only high coverage of preventive measures compliance coupled with high coverage of testing, tracing and isolation would result in a decrease on Rt.[14] Similar to the documentation on preventive behaviours, there is no periodic information of these three indicators yet.

Such limitation on surveillance and information system intensifies needs on Indonesia health systems strengthening. Recent evidence outlines test, tracing and isolation are effective in suppressing COVID-19 transmission.[8,17,18] Minimizing testing and tracing delay, less than four days with coverage of 80% close contacts could prevent and reduce onwards transmission.[18] The evidence base for tracing delay and tracing ratio in Indonesia is hindered by limited of data. But the frail disease surveillance and detected reporting delays implies testing delay remains an issue, and contact tracing is inadequate. No or weak contact tracing would let the chain of transmission free and undetected; opening possibility of transmission would grow exponentially.[19]

That we need to more is indisputable. The vaccine is not a magic bullet; it is a long-term control measure and should be a complete series of careful and precise examinations. Indonesia will also likely require high coverage of vaccination to achieve herd immunity. At present, if there is no significant improvement in the coverage of preventive measures in the population and disease surveillance system, our hospital will be overwhelmed, and case fatality will be devastating.

REFERENCES

1. Badan Pusat Statistik. Statistik Indonesia 2019. Jakarta: Badan Pusat Statistik; 2019.
2. Mboi N, Murty Surbakti I, Trihandini I, et al. On the road to universal health care in Indonesia, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018; 392 (10147):581-91.
3. Satuan Tugas Penanganan COVID-19. Perkembangan kasus terkonfirmasi positif COVID-19 per-hari. 2020. https://covid19.go.id/peta-sebaran2020).
4. Muthiariny D. Jokowi admits Indonesia's COVID-19 fatality rate higher than global average. Tempo. 2020 2 September 2020.
5. Bayham J, Fenichel EP. Impact of school closures for COVID-19 on the US health-care workforce and net mortality: a modelling study. Lancet Publ Health. 2020; 5(5): e271-e8.
6. Lau H, Khosrawipour V, Kocbach P, et al. The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China. J Travel Med. 2020; 27(3).
7. Ferguson N, Laydon D, Nedjati Gilani G, et al. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. 2020.
8. Kucharski AJ, Klepac P, Conlan AJK, 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. Lancet Infect Dis. 2020.
9. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis. 2020.
10. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020; 395(10242):1973-87.
11. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel

coronavirus (SARS-CoV2). Science 2020.
12. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 73. World Health Organization; 2020.
13. Ariawan I, Riono P, Farid MN, Jusril H, Wahyuningsih W. COVID-19 di Provinsi DKI Jakarta. Jakarta Indonesia; 2020.
14. Ariawan I, Riono P, Farid MN, Jusril H. An epidemiologic model for COVID-19 post-PSBB in Indonesia. Jakarta: FKM UI, 2020.
15. Ariawan I, Riono P, Farid MN, Jusril H. Pembatasan sosial di Indonesia: Apakah ada dampaknya terhadap epidemi COVID-19? Jakarta; 2020.
16. Phillips DL, Clancy KJ. Some effects of "social desirability" in survey studies. Am J Sociol. 1972; 77(5):921-40.
17. Cheng H-Y, Jian S-W, Liu D-P, et al. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med. 2020.
18. Kretzschmar ME, Rozhnova G, Bootsma MCJ, van Boven M, van de Wijgert JHHM, Bonten MJM. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. Lancet Publ Health. 2020;5(8):e452-e9.
19. MacIntyre CR. Case isolation, contact tracing, and physical distancing are pillars of COVID-19 pandemic control, not optional choices. Lancet Infect Dis. 2020; 20(10):1105-6.

Dilemma of Prioritising Health and the Economy During COVID-19 Pandemic in Indonesia

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Since the detection of the first confirmed case of coronavirus disease 2019 (COVID-19) in early March 2020, 248,852 cases have been detected in Indonesia by 21 September 2020. The case fatality rate (CFR) of COVID-19 in Indonesia is 3.9%,[1] a much lower percentage compared to the CFR in March 2020 (8.9%).[2] The number of daily new confirmed cases exceeded 4,000 in September 2020,1 although many still argued that COVID-19 was still underdetected in Indonesia.[3] In mid-September, Indonesia only had 5.37 tests per thousand population, which was among the lowest in the world.[4]

It is clear that most governments in the world underestimated the risks of rapid spread of COVID-19. The countries were generally reactive later in the crisis response.[5] Many countries are, however, in dilemma of protecting the health of the citizens and prioritising economy recovery.[6] Early in pandemic, the board of professors of Universitas Indonesia wrote a letter to the president of Indonesia and the the head of COVID-19 Task Force to suggest prompt implementation of partial lockdown and to provide financial assistance for necessitous citizens at the same time. The implementation of full large-scale social restriction / *Pembatasan Sosial Berskala Besar* (PSBB) were chosen as temporary measure followed by an early transition to the new normal era. There was, however, flawed perception of the current COVID-19-related condition in Indonesia due to the use of the term 'new normal', which led to the appearance of large clusters after the restrictions were eased.3 Family cluster with different clinical symptoms was also reported in Indonesia.[7] Many parties have restarted economic activities during the never-ending first wave in Indonesia and thought that the COVID-19 vaccine was available in the near future.[8] COVID-19 pandemic resulted in different economic impacts depending on the types of workers. Working from home is a feasible activity to many office workers, whereas workers in industrial, retail, transport, and tourism fields suffered a significant decrease in work.[5] In early period of the pandemic, Indonesian government has already estimated that millions would fall into poverty and lose their jobs during COVID-19 pandemic.[9]

Prior to the pandemic, Indonesia only had 2.7 intensive care unit (ICU) beds per 100,000 people and the ratio was among the lowest in Asia.[2] In early pandemic, only 50% of state-owned hospitals were equipped with mechanical ventilators.[10] Currently, the mechanical ventilators are still limited in number and unevenly distributed. There is also international shortage of personal protective equipments (PPE) for healthcare workers.[6]

Many healthcare workers in Indonesia had to buy their own PPE or rely on donations. It is also known that at least 100 doctors have died from COVID-19 in Indonesia.

In the capital city, more than 75% of ICU were already occupied in early September 2020. Although the projected increase in ICU bed occupancy level is accompanied by the effort to increase the capacity of ICU in Jakarta, the number of patients requiring intensive care was estimated to be higher than the total number of ICU beds in the city.[11] On the other hand, although new isolation facilities are constantly prepared by the government, the number of isolation beds for COVID-19 patients were also projected to outnumber the amount of available beds in Jakarta. Without additional intervention, number of local patients requiring isolation wards may reach 4,807 in 6 October 2020, whereas such high amount of isolation beds is only available for use in 8 October 2020.[11] Therefore, the local government of Jakarta decided to implement full form of PSBB for a second time starting from 14 September 2020 as an emergency brake measure.

HEALTH VS. ECONOMY

Health is crucial for the prosperity of any society.[6] World Health Organisation suggested dual-track health system management during the pandemic. Countries should focus on both COVID-19 and other forms of essential healthcare.[12] The failure to suppress the spread of COVID-19 may have adverse impact on the economy. Poor health is estimated to reduce global gross domestic product (GDP) by 15% annually through premature deaths as well as potential loss of productivity of the working-age citizens.[13] In general, pandemics also depress economy through decrease in both supply and demand.[14]

It is true that we should not forget the past, but we should learn from it instead. The analysis of data from flu pandemic in 1918 suggested that areas that were affected more severely by the flu pandemic had steep and continuous drop in real economic activity. The severely affected areas had relative decrease in consumption of durable goods, bank assets, manufacturing production, and manufacturing employment.[15]

Areas that implemented early non-pharmaceutical health interventions extensively did not suffer from adverse economic impact over the medium term. Moreover, areas with early action had a relative increase in real economic activity following the pandemic. In other words, pandemics may have substantial economic costs, but non-pharmaceutical health interventions will result in improved economic outcomes as well as lower mortality rates. The interventions implemented during the pandemic a century ago were similar to those implemented during COVID-19 pandemic, including restrictions on business hours, quarantines of suspected cases, prohibition of public gathering, as well as closures of theatres, schools and places of worship. Aggressiveness and speed of interventions are essential[15], whereas the relaxation of containment measures may potentially cause health consequences.[6] Taiwan may be a successful role model for pandemic management despite its proximity to mainland China where the outbreak began. During the pandemic, the government of Taiwan planned an early deployment of epidemic control action. The epidemic has been well-controlled since April 2020. Afterwards, the manufacturing purchasing managers index in July rebounded to the highest point in the previous six months. Merchandise exports and consumer confidence also rose after the economy was battered by COVID-19.[16]

During COVID-19 pandemic, governments generally require two policy instruments, namely mitigating policy, and post-COVID-19 recovery and rejuvenation policy. The former will involve containment measures, provision of PPEs and incentives for healthcare workers, and enhancement of testing and isolation facilities. Post-COVID-19 recovery and rejuvenation policy will ensure lockdowns and physical distancing in the society, since previous systematic review and meta-analysis concluded that physical distancing of 1 m or more during COVID-19 pandemic led to lower transmission of virus with moderate certainty compared to distance less than 1 m (pooled adjusted odds ratio 0.18, 95% confidence interval 0.09 to 0.38).[17]

By prioritising health, we could reduce health inequity, improve resilience, and greater

economic well-being. We could achieve 70% of the economic benefits with adoption of healthier behaviours, cleaner environments, as well as improved access to preventive medicine and vaccine. On the other hand, treatment of diseases only contribute to the remainder of economic benefit.[13]

EVIDENCE-BASED SUGGESTION

We should not cry over spilt milk due to the lack of early and aggressive interventions in early 2020 in Indonesia. Health should still be prioritised because it is an important aspect of our lives for our economy. The target of enhancement of containment measures, provision of PPEs, and testing and isolation facilities should be achieved earlier and be more than the estimated demand.

REFERENCES

1. Satuan Tugas Penanganan COVID-19. Peta sebaran Gugus Tugas Percepatan Penanganan COVID-19 [Internet]. 2020 [cited 2020 Sep 21]. p. 1. Available from: https://covid19.go.id/peta-sebaran.
2. Setiati S, Azwar MK. COVID-19 and Indonesia. Acta Med Indones. 2020;52(1):84–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32291377.
3. Souisa H, Wibawa T. Indonesia struggles with rising coronavirus infections as tests become commercialised. ABC News. 2020 Jul 17; Available from: https://www.abc.net.au/news/2020-07-18/indonesia-covid-19-new-normal-commercialisation-test/12459496.
4. Oxford Martin School, University of Oxford. Total COVID-19 tests per 1,000 people [Internet]. Our World in Data. 2020 [cited 2020 Sep 13]. Available from: https://ourworldindata.org/grapher/full-list-cumulative-total-tests-per-thousand?tab=table&time=2020-02-20.latest.
5. Pak A, Adegboye OA, Adekunle AI, Rahman KM, McBryde ES, Eisen DP. Economic consequences of the COVID-19 outbreak: the need for epidemic preparedness. Front Public Heal. 2020 May 29;8. Available from: https://www.frontiersin.org/article/10.3389/fpubh.2020.00241/full.
6. Moti UG, Goon D Ter. Novel Coronavirus Disease: A delicate balancing act between health and the economy. Pakistan J Med Sci. 2020 May;36(COVID19-S4):S134–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32582333.
7. Soedarsono S. A Family cluster of Coronavirus Disease (COVID-19) infection with different clinical manifestations. Acta Med Indones. 2020;52(2):155–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32778630.
8. The Jakarta Post. COVID-19: Ombudsman slams govt for "focusing too much on economic recovery". The Jakarta Post. 2020 Aug 31; Available from: https://www.thejakartapost.com/news/2020/08/31/covid-19-ombudsman-slams-govt-for-focusing-too-much-on-economic-recovery.html.
9. Akhlas A. Millions to lose jobs, fall into poverty as Indonesia braces for recession. The Jakarta Post [Internet]. 2020 Apr 15; Available from: https://www.thejakartapost.com/news/2020/04/14/millions-to-lose-jobs-fall-into-poverty-as-indonesia-braces-for-recession.html.
10. Aldin I. 50% ICU RS Pemerintah tanpa ventilator, Erick akan cari ke ujung dunia. Katadata [Internet]. 2020 Jul; Available from: https://katadata.co.id/happyfajrian/berita/5e9a41f6105bd/50-icu-rs-pemerintah-tanpa-ventilator-erick-akan-cari-ke-ujung-dunia.
11. Tim Detikcom. Grafik mengkhawatirkan ini yang bikin PSBB ketat DKI diberlakukan lagi. detikNews [Internet]. 2020 Sep 10; Available from: https://news.detik.com/berita/d-5166864/grafik-mengkhawatirkan-ini-yang-bikin-psbb-ketat-dki-diberlakukan-lagi.
12. WHO Europe. Strengthening and adjusting public health measures throughout the COVID-19 transition phases: Policy considerations for the WHO European Region [Internet]. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/technical-guidance/2020/strengthening-and-adjusting-public-health-measures-throughout-the-covid-19-transition-phases.-policy-considerations-for-the-who-european-region,-24-a.
13. Remes J, Dewhurst M, Woetzel J. Research: poor health reduces global GDP by 15% each year. Harvard Business Rev. 2020 Jul 8; Available from: https://hbr.org/2020/07/research-poor-health-reduces-global-gdp-by-15-each-year.
14. Eichenbaum M, Rebelo S, Trabandt M. The Macroeconomics of Epidemics. Cambridge, MA; 2020 Mar. Available from: http://www.nber.org/papers/w26882.pdf.
15. Correia S, Luck S, Verner E. Fight the pandemic, save the economy: Lessons from the 1918 flu. Lib Str Econ. Available from: https://libertystreeteconomics.newyorkfed.org/2020/03/fight-the-pandemic-save-the-economy-lessons-from-the-1918-flu.html.
16. Focus Economics. Taiwan economic outlook [Internet]. [cited 2020 Sep 21]. Available from: https://www.focus-economics.com/countries/taiwan.
17. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020;395(10242):1973–87. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673620311429.

Clinical Profile of Elderly Patients with COVID-19 Hospitalized in Indonesia's National General Hospital

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ABSTRAK

Latar belakang: *sebanyak 38.6% kasus kematian pasien COVID-19 di Indonesia terjadi di populasi lansia. Data mengenai profil klinis pasien rawat inap lansia dengan COVID-19 masih tidak ada. Padahal kelompok pasien ini adalah pasien risiko tinggi selama pandemi ini yang memerlukan perhatian lebih.* ***Metode:*** *studi deskriptif ini menggunakan data lengkap pasien lansia dengan COVID-19 yang dirawat inap di Rumah Sakit Umum Pusat Nasional Cipto Mangunkusumo (RSUPN Cipto Mangunkusumo) dari April hingga akhir Agustus 2020. Data termasuk karakteristik klinis, gejala, komorbiditas, multimorbiditas dan luaran mortalitas pasien.* ***Hasil:*** *di populasi pasien lansia (n=44), mayoritas berusia di antara 60-69 tahun (68%), berjenis kelamin laki-laki (66%), dan tidak memiliki riwayat kontak erat dengan pasien COVID-19 sebelumnya (86%). Gejala tersering ialah demam, batuk, dan sesak yang merupakan gejala khas COVID-19, sedangkan penyakit kronis tersering adalah diabetes melitus, hipertensi, dan keganasan. Multimorbiditas ditemukan hanya di 14% pasien lansia, dan para pasien tersebut bertahan hidup pasca infeksi virus SARS-CoV-2. Angka kematian pasien lansia rawat inap dengan COVID-19 di studi ini adalah 23%, dan 90% dari kasus kematian berjenis kelamin laki-laki.* ***Kesimpulan:*** *pasien laki-laki mendominasi kasus terkonfirmasi dan kasus kematian lansia dengan COVID-19. Gejala khas COVID-19 hanya ditemukan di sekitar setengah pasien penelitian. Pasien yang meninggal dunia memiliki persentase gejala khas lebih tinggi. Gejala tidak khas pun mungkin ditemukan di pasien lansia. Immunosenescence dan fungsi imunoregulasi jenis kelamin tertentu dihipotesiskan memiliki peran penting dalam menyebabkan kematian lansia di studi ini.*

Kata kunci: *profil klinis, lansia, pasien geriatri, COVID-19, Indonesia.*

ABSTRACT

Background: *older people contributed to 38.6% of death cases related to COVID-19 in Indonesia. Data regarding clinical profile of hospitalised elderly with COVID-19 in Indonesia were still lacking. Older people are at-risk population in the pandemic, whom we should pay attention to.* ***Methods:*** *this single centre descriptive study utilised complete data of elderly inpatients with COVID-19 in Indonesia's national general hospital from April to late August 2020. The data consisted of clinical characteristics, symptoms, comorbidities, multimorbidity, and mortality outcome.* ***Results:*** *among elderly patients (n=44), a majority of patients were aged 60-69 years (68%), were male (66%), and had no history of close contact with COVID-19 patient (86%). The most common*

symptoms were fever, cough and shortness of breath (classic symptoms of COVID-19), whereas the most common chronic diseases were diabetes mellitus, hypertension, and malignancy. Multimorbidity was only found in 14% of patients, all of whom remained alive following SARS-CoV-2 infection. The death rate among elderly inpatients with COVID-19 in this study was 23%, and male older adults contributed to 90% of death cases. ***Conclusion:*** *male patients dominated both confirmed cases and death cases among elderly with COVID-19. Classic symptoms of COVID-19 were only found in about half of the study patients. Non-survivors had higher percentage of the classic symptoms of COVID-19 than survivors. Atypical COVID-19 presentations are possible in older adults. We postulated that immunosenescence and sex-specific immunoregulatory function play an important role in causing death in this study cohort.*

Keywords: *clinical profile, elderly, geriatric patient, COVID-19, Indonesia.*

INTRODUCTION

Indonesia faced challenges in tackling coronavirus disease 2019 (COVID-19). The pandemic itself is still an ongoing problem in many parts of the world. There is no sign of decrease in number of new cases in Indonesia, which exceeded 3,000 in late August. In late March 2020, the nation's case fatality rate (CFR) reached 8.9%[1], whereas the rate was 4.3% in late August.[2] Despite the decrease, it was still higher than the global case fatality rate.

Among confirmed cases in late August in Indonesia, 11.2% were elderly patients aged 60 years and above. Older people also contribute to 38.6% of death cases related to COVID-19 nationwide.[2] A hospital-based report from Hainan, China, stated that only 5.26% of elderly with COVID-19 died. The most common symptoms were fever and cough. Only a minority of elderly had co-morbidities, such as diabetes and diabetes.[3] However, data regarding clinical profile of hospitalised elderly with COVID-19 in Indonesia were lacking. Older people are at-risk population in the pandemic,[4] whom we should pay attention to. Indonesia's national general hospital is one of COVID-19 referral centres with integrated care and specialised isolation ward for the patients, including elderly inpatients with COVID-19.

We aimed to provide a descriptive study results of clinical profile of elderly inpatients with COVID-19 in Indonesia's national general hospital. This may in turn inform Indonesian physicians of the possible presentations and sex-specific difference in outcome of elderly with COVID-19.

METHODS

This observational descriptive study utilised inpatient data of Cipto Mangunkusumo Hospital, Indonesia's national general hospital, from April to late August 2020. The data of elderly inpatients aged 60 years and older with COVID-19 consisted of clinical characteristics, symptoms, comorbidities, and mortality outcome. The data were inputted and filled in by physicians to electronic and handwritten medical record, respectively. The inclusion criterion was complete data of elderly inpatients with COVID-19.

COVID-19 confirmation was based on gold-standard laboratory test, reverse transcription polymerase chain reaction (RT-PCR). Clinical characteristics consisted of age (classified into 60-69 years; and 70 years and older), sex (female or male), history of close contact with COVID-19 patients, and outcome. We took into account fever, cough, shortness of breath, sore throat, rhinorrhoea, anosmia, nausea, vomitting, diarrhoea, abdominal pain, myalgia and malaise as symptoms reported by the patients. Underlying chronic diseases included diabetes mellitus, hypertension, cardiovascular disease, chronic kidney disease (CKD), malignancy, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis (TB), cerebrovascular disease. We also gathered data in regards to multimorbidity of elderly patients. Multimorbidity was defined as the presence of 2 or more chronic diseases in the same individual. We recorded the data related to history of close contact, symptoms, and comorbidites as "yes" if present and "no" if absent. Descriptive statistical analysis utilised IBM SPSS Statistics Version 20 and the results were subsequently presented as number of cases and percentage.

Table 1. Clinical characteristics and symptoms of elderly patients with COVID-19 hospitalised in Indonesia's national general hospital.

Variables	All elderly patients n (%)	Survivors (n=34) n (%)	Non-survivors (n=10) n (%)
Clinical Characteristic			
Age group			
- 60-69 years	30 (68)	24 (71)	6 (60)
- 70 years and above	14 (32)	10 (29)	4 (40)
Sex, Male	29 (66)	20 (59)	9 (90)
History of close contact with COVID-19 patient			
- No	38 (86)	28 (82)	10 (100)
- Yes	6 (14)	6 (18)	0 (0)
Symptoms			
Fever			
- No	18 (41)	14 (41)	4 (40)
- Yes	26 (59)	20 (59)	6 (60)
Cough			
- No	18 (41)	14 (41)	4 (40)
- Yes	26 (59)	20 (59)	6 (60)
Shortness of breath			
- No	19 (43)	15 (44)	4 (40)
- Yes	25 (57)	19 (56)	6 (60)
Sore throat			
- No	36 (82)	26 (76)	10 (100)
- Yes	8 (18)	8 (24)	0 (0)
Rhinorrhoea			
- No	43 (98)	33 (97)	10 (100)
- Yes	1 (2)	1 (3)	0 (0)
Anosmia			
- No	44 (100)	34 (100)	10 (100)
- Yes	0 (0)	0 (0)	0 (0)
Nausea			
- No	39 (89)	30 (88)	9 (90)
- Yes	5 (11)	4 (12)	1 (10)
Vomitting			
- No	40 (91)	31 (91)	9 (90)
- Yes	4 (9)	3 (9)	1 (10)
Diarrhoea			
- No	37 (84)	30 (88)	7 (70)
- Yes	7 (16)	4 (12)	3 (30)
Abdominal pain			
- No	40 (91)	30 (88)	10 (100)
- Yes	4 (9)	4 (12)	0 (0)
Myalgia			
- No	41 (93)	32 (94)	9 (90)
- Yes	3 (7)	2 (6)	1 (10)
Malaise			
- No	23 (52)	17 (50)	6 (60)
- Yes	21 (48)	17 (50)	4 (40)

The study has been approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia with reference number KET-419/UN2F1/ETIK/PPM.00.02/2020.

RESULTS

We collected data from 44 elderly patients in this study. The death rate among this cohort was 23%. Among all elderly patients, a majority of patient were aged 60-69 years (68%), were male (66%), and had no history of close contact with COVID-19 patient (86%). (**Table 1**) The classic COVID-19 symptoms of fever, cough and shortness of breath were only present in 59%, 59%, and 57% of elderly patients, respectively. Nearly half of the patients had malaise. Most elderly patients did not complain of sore throat, rhinorrhoea, anosmia, nausea, vomitting, diarrhoea, abdominal pain, and myalgia.

There was a higher proportion of elderly aged 70 years and older among non-survivors compared to the survivors (40% vs 30%). Ninety percent of non-survivors were male patients. Diarrhoea were also present in 30% of non-survivors, whereas it was reported by only 11.8% of survivors.

Multimorbidity was only found in 14% of patients, all of whom remained alive following SARS-CoV-2 infection. The most common chronic diseases found in elderly inpatients with COVID-19 were diabetes mellitus (11%), hypertension (14%), and malignancy (7%). (**Table 2**).

Table 2. Chronic diseases of elderly patients with COVID-19 hospitalised in Indonesia's national general hospital.

Variables	All elderly patients n (%)	Survivors (n=34), n (%)	Non-survivors (n=10), n (%)
Diabetes mellitus			
- No	39 (89)	29 (85)	10 (100)
- Yes	5 (11)	5 (15)	0 (0)
Hypertension			
- No	38 (86)	28 (82)	10 (100)
- Yes	6 (14)	6 (18)	0 (0)
Cardiovascular disease			
- No	43 (98)	33 (97)	10 (100)
- Yes	1 (2)	1 (3)	0 (0)
Chronic kidney disease			
- No	42 (95)	32 (94)	10 (100)
- Yes	2 (5)	2 (6)	0 (0)
Malignancy			
- No	41 (93)	32 (94)	9 (90)
- Yes	3 (7)	2 (6)	1 (10)
Chronic obstructive pulmonary disease			
- No	44 (100)	34 (100)	10 (100)
- Yes	0 (0)	0 (0)	0 (0)
Asthma			
- No	44 (100)	34 (100)	10 (100)
- Yes	0 (0)	0 (0)	0 (0)
Tuberculosis			
- No	42 (95)	33 (97)	9 (90)
- Yes	2 (5)	1 (3)	1 (10)
Cerebrovascular disease			
- No	43 (98)	33 (97)	10 (100)
- Yes	1 (2)	1 (3)	0 (0)
Multimorbidity (≥2 chronic diseases in the same individual)			
- No	38 (86)	28 (82)	10 (100)
- Yes	6 (14)	6 (18)	0 (0)

DISCUSSION

The death rate among hospitalised older adults with COVID-19 in this study was much higher than the national COVID-19 case fatality rate among Indonesian elderly (23% vs 14.9%).[2] Not only was male sex predominant among confirmed cases of COVID-19 in elderly population in this study, 90% of non-survivors were also of male sex. A study utilising data of 17,278,392 adults suggested that male sex itself is associated with COVID-19-related death (hazard ratio (HR) 1.59, 95% CI 1.53 to 1.65). The study also showed that estimated HR for COVID-19-related death also increases in older age groups.[4]

There were several mechanisms that could possibly explain the link between male sex and unfavourable disease outcome. Both ACE2 and transmembrane serine protease-2 (TMPRSS2) are crucial for SARS-CoV-2 viral entry in human cells.[5] Since ACE2 gene is located on the X chromosome, alleles that confer resistance to COVID-19 may be present, explaining the lower adverse outcome among female patients.[6] Different outcome of the disease based on sex category can also be explained by different immunoregulatory functions of testosterone and oestrogen sex hormones.[7] In general, there is different response to many DNA and RNA viral infections in males compared to females.[8] Testosterone's control of TMPRSS2 expression has been suggested to contribute to male predominance in terms of unfavourable outcomes in COVID-19. Androgen receptor activity is required for the transcription of TMPRSS2 gene.[9] Furthermore, immune system of male individuals respond to the infection less robustly. Ageing males have a more dramatic decrease in total amount of B and T cells compared to females. In addition, ageing males experience higher increases in senescent CD8+ T effector memory cells. Similar to COVID-19 data, epidemiological data of SARS-CoV-1 and MERS-CoV infection also suggested different disease outcome based on sex category.[8]

As one ages, disruption of both innate and adaptive arms of the immune system has been reported.[10] Ageing is characterised by a progressive dysfunction of several compartments of the immune system, namely immunosenescence, including immunodeficiency and smouldering inflammation.[11] Immunosenescence of COVID-19 patients may in turn promote viral-induced cytokine storm leading to systemic problems, and life-threatening respiratory failure.10 In addition, abnormal ciliary function may impair SARS-CoV-2 viral particle clearance in the elderly.[12]

The disease has been widespread in Indonesia. There was increasing evidence that several patients with COVID-19 have only mild symptoms or are asymptomatic. However, there are difficulties in detecting the asymptomatic infections.[13] Since almost all elderly in this study had no history of close contact with confirmed cases, older adults as well as their caregivers and relatives should really take extra precautions against COVID-19. Moreover, family cluster has been reported in Indonesia and asymptomatic person may potentially transmit the virus.[14]

In this study, only approximately 50% elderly inpatients with COVID-19 presented with classic symptoms of COVID-19 (fever, cough, and shortness of breath). In addition, it should be noted that the percentages of patients complaining of fever, cough, and shortness of breath were higher in non-survivors. This highlights the possibility of atypical presentation of COVID-19 among older adults. Albeit possible, the most common symptoms of COVID-19 in both elderly and non-elderly patients are still fever and cough.[3] Older people are generally already at risk for higher morbidity and mortality due to infection. However, as a cardinal sign of infection, fever may be absent or blunted in elderly patients. The absence of or blunted response to fever may result in diagnostic delay in this population.15 The delay in diagnosis may in turn cause further spread of COVID-19.[16]

The most common chronic diseases of confirmed cases and death cases in older adults in this study were similar to the overall national data, namely hypertension and diabetes mellitus.2 Similarly, hypertension (43.8%) and diabetes mellitus (25.7%) were also the most common underlying chronic diseases in elderly patients with COVID-19 according to a multicentre study in China.[17] A hospital in Hainan, China,

reported that only 27.78% of elderly with COVID-19 had hypertension, whereas it was 16.67% for diabetes.[3] Most underlying chronic diseases were associated with increased risk for death of COVID-19 patients, including diabetes mellitus, cardiovascular disease, kidney disease, respiratory disease (including severe asthma) and history of malignancy.[4] Based on our study and the previous reports, the co-morbidities were found only in a minority of elderly with COVID-19.

An analysis of adult data from UK Biobank (n=428,199) suggested that multimorbidity, especially cardiometabolic multimorbidity, was associated with increased risk for developing COVID-19.[18] As multimorbidity was not the prominent feature of non-survivors in our study, we postulated that immunosenescence and sex-specific immunoregulation play an important role in causing death in this study cohort.

To date, we believe that our study is the first descriptive study focusing on the clinical profile of elderly inpatients with COVID-19 in Indonesia. It is also among the first descriptive studies with similar topic in Southeast Asia. On the other hand, we acknowledge the limitations of this study. The number of patients in this study was still limited. The preliminary data were not consecutive nor randomised. This study relied on successful collection of complete data of patients from the medical record. However, we believe that there may not be remarkable differences between the data presented in this study and the data gathered with extension of data collection period. This article may act as a thought-provoking manuscript to increase the awareness and possibilities pertaining to elderly inpatients with COVID-19. Future studies with similar focus and larger sample size have yet to be conducted.

CONCLUSION

The death rate among elderly inpatients with COVID-19 in this study was 23%, dominated by male patients. Fever, cough, and shortness of breath were only found in about half of elderly with COVID-19, but non-survivors had higher percentage of the classic symptoms of COVID-19 than survivors. The most common underlying chronic diseases were diabetes mellitus and hypertension. We postulated that immunosenescence and sex-specific immunoregulatory function play an important role in causing death in this study cohort.

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REFERENCES

1. Setiati S, Azwar MK. COVID-19 and Indonesia. Acta Med Indones [Internet]. 2020 Jan 1;52(1):84–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32291377.
2. Satuan Tugas Penanganan COVID-19. Peta sebaran Gugus Tugas Percepatan Penanganan COVID-19 [Internet]. 2020 [cited 2020 Aug 29]. p. 1. Available from: https://covid19.go.id/peta-sebaran.
3. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020;80(6):e14–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32171866.
4. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32640463.
5. Azwar MK, Kirana F, Kurniawan A, Handayani S, Setiati S. Gastrointestinal presentation in COVID-19 in Indonesia: A case report. Acta Med Indones. 2020;52(1):63–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32291373.
6. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363–74. Available from: http://www.nature.com/articles/s41577-020-0311-8.
7. Taneja V. Sex hormones determine immune response. Front Immunol. 2018;9. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2018.01931/full.
8. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-based differences in susceptibility to severe acute respiratory syndrome Coronavirus infection. J Immunol. 2017;198(10):4046–53. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.1601896.
9. Pozzilli P, Lenzi A. Commentary: testosterone, a key hormone in the context of COVID-19 pandemic. Metabolism. 2020;108:154252. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0026049520301165.

10. 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):1599–608. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32557332.
11. Bencivenga L, Rengo G, Varricchi G. Elderly at time of CoronaVirus disease 2019 (COVID-19): possible role of immunosenescence and malnutrition. Gero Science. 2020;42(4):1089–92. Available from: http://link.springer.com/10.1007/s11357-020-00218-9.
12. Ho JC, Chan KN, Hu WH, et al. The effect of aging on nasal mucociliary clearance, beat frequency, and ultrastructure of respiratory cilia. Am J Respir Crit Care Med. 2001;163(4):983–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11282777.
13. Gao Z, Xu Y, Sun C, et al. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect. 2020 May 15; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32425996.
14. Soedarsono S. A family cluster of Coronavirus disease (COVID-19) infection with different clinical manifestations. Acta Med Indones. 2020;52(2):155–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32778630.
15. Norman DC. Fever in the elderly. Clin Infect Dis. 2000;31(1):148–51. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/313896.
16. Rong X, Yang L, Chu H, Fan M. Effect of delay in diagnosis on transmission of COVID-19. Math Biosci Eng. 2020;17(3):2725–40. Available from: http://www.aimspress.com/article/10.3934/mbe.2020149.
17. Guo T, Shen Q, Guo W, et al. Clinical characteristics of elderly patients with COVID-19 in Hunan Province, China: A multicenter, retrospective study. Gerontology. 2020;1–9. Available from: https://www.karger.com/Article/FullText/508734.
18. McQueenie R, Foster HME, Jani BD, et al. Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort. In: Feng Y-M, editor. PLoS One. 2020;15(8):e0238091. Available from: https://dx.plos.org/10.1371/journal.pone.0238091.

Test, Trace, and Treatment Strategy to Control COVID-19 Infection Among Hospital Staff in a COVID-19 Referral Hospital in Indonesia

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ABSTRAK

Latar belakang: *infeksi COVID-19 disebabkan oleh virus korona baru. Salah satu strategi yang paling banyak digunakan untuk mengendalikan penyebaran COVID-19 adalah 3T (test, trace, and treatment). Penelitian ini bertujuan untuk mengevaluasi strategi 3T pengendalian infeksi COVID-19 di Rumah Sakit Rujukan COVID-19 Depok, Jawa Barat, Indonesia.* ***Metode:*** *penelitian potong lintang yang dilakukan di RS Universitas Indonesia. Penelitian dilakukan pada bulan Juni 2020 dengan 742 partisipan (anggota staf) menggunakan data sekunder hasil uji polymerase chain reaction (PCR). Kami menyajikan data dalam bentuk deskriptif dan melakukan analisis bivariat menggunakan uji chi-square/ Fischer untuk data kategorikal.* ***Hasil:*** *hasil tes PCR positif pada 83 (11,1%) peserta, dengan rasio kasus per penelusuran 1:24 dan 1:2 masing-masing pada fase pelacakan pertama dan ketiga. Grafik kasus COVID-19 untuk peserta menurun seiring dengan penerapan strategi 3T. Tingkat positif pada pelacakan tahap pertama adalah 20% dan menurun menjadi 5% pada pelacakan tahap ketiga. Staf dengan hasil tes yang dikonfirmasi positif disarankan untuk mengisolasi diri mereka sendiri (rumah sakit atau isolasi sendiri). Isolasi rumah sakit ditemukan terkait dengan durasi konversi tes PCR ($p<0,001$).* ***Kesimpulan:*** *strategi 3T efektif untuk mengendalikan penyebaran COVID-19. Penerapan strategi ini harus dilakukan bersamaan dengan kewaspadaan kesehatan lainnya untuk mengurangi risiko penyebaran infeksi.*

Keywords: *strategi 3T, COVID-19, tes PCR, RS. Universitas Indonesia.*

ABSTRACT

Background: *COVID-19 infection is caused by a novel coronavirus. One of the most used strategies that can be used to control the spread of COVID-19 is the 3T (test, trace, and treatment) strategy. This study aimed to evaluate the 3T strategy to control COVID-19 infection in a COVID-19 Referral Hospital in Depok, West Java, Indonesia.* ***Methods:*** *this is a cross-sectional study conducted at the University of Indonesia Hospital. The study was conducted in June 2020 with 742 participants (staff members) using secondary data from polymerase chain reaction (PCR) test results. We presented data in the descriptive form and performed bivariate analysis using the chi-square/Fischer test for categorical data.* ***Results:*** *the PCR test results were positive in 83 (11.1%) participants, with a case-per-tracing ratio of 1:24 and 1:2 in the first and third phases of tracing, respectively. The COVID-19 case graph for the participants decreased along with the implementation of the 3T strategy. The positivity rate in the first phase of tracing was 20% and decreased to 5% in the third phase of tracing. Staff with*

confirmed positive test results were advised to isolate themselves (hospital or self-isolation). Hospital isolation was found to be associated with the duration of PCR test conversion (p<0.001). ***Conclusion:*** *the 3T strategy is effective for controlling the spread of COVID-19. The strategy should be implemented simultaneously with other health precautions to reduce the risk of spreading infection.*

Keywords: *3T strategy, COVID-19, PCR test, Universitas Indonesia Hospital.*

INTRODUCTION

COVID-19 is a respiratory infection caused by the novel coronavirus or SARS-CoV-2. It originated in the animal and seafood market of Hubei Province, China in December 2019.[1] According to the World Health Organization (WHO), COVID-19 affected 219 countries, infected 16,558,289 people, and caused 656,093 deaths.[2] Indonesia is one of the countries with the highest infection rates. Data from the Indonesian Ministry of Health showed that as of July 29, 2020, there were 104,432 COVID-19 confirmed cases in Indonesia and 4,975 deaths.[3]

Depok is a suburban city located near Jakarta and at risk of being the center of infection due to high mobility and a higher number of COVID-19 cases in neighboring cities. On July 29, 2020, there were 1,172 confirmed cases and 45 deaths in Depok.[4] To increase the diagnostic capacity of close contacts of confirmed COVID-19 patients and people or patients under surveillance, the Government of Depok allocated 3,600 additional polymerase chain reaction (PCR) tests for Depok residents. The University of Indonesia Hospital was appointed to perform these additional PCR tests.

Hospital staff are susceptible to infection in this pandemic due to their close contact with infected patients. For example, in the early COVID-19 pandemic, it was found that 1.1% of health workers in tertiary hospitals in Wuhan, China were confirmed to be positive for SARS-CoV-2.[5] Similar findings were also observed in Indonesia. In June 2020, 75 health workers were confirmed cases in East Java, of whom 12 were medical residents.[6] In late May 2020, Depok General Hospital was forcibly closed because 27 staff members were found to be positive for SARS-CoV-2.[7] The University of Indonesia Hospital is one of the referral hospitals of COVID-19 in Depok and dealing with similar situations. Therefore, the University of Indonesia Hospital must devise a way that not only focuses on controlling infection transmission, but also mitigates the risk of becoming an infection epicenter.

One of the most used strategies that can be used to control COVID-19 spread is the test, trace, and treatment (3T) strategy. This strategy is designed to control the infection chain of the disease by identification of COVID-19 cases using laboratory tests, tracing close contacts of confirmed cases, and advising them to isolate to prevent further spread of infection.[8] This article discusses the implementation of a 3T strategy to control the spread of infection among the staff of University of Indonesia Hospital.

METHODS

A cross-sectional design was used in this study. The study was conducted at the University of Indonesia Hospital in June 2020. The data were collected from the secondary data from the PCR test results of the staff members of the Hospital. A total of 742 participants were included in this study. All participants included the hospital staff of University of Indonesia Hospital (health workers and non-health workers). We present data in the descriptive form and performed bivariate analysis using the chi-square or Fischer test for categorical data. The Ethical Committee of Universitas Indonesia Hospital approved this study (Reference no. 002/SKPE/KKO/2020/00).

The Universitas Indonesia Hospital conducted PCR testing during June 19-23, 2020. PCR tests were carried out on staff members who were registered and screened through electronic forms provided by the Universitas Indonesia Hospital. The registration form included identity, screening for symptoms, contact history, risk of transmission, comorbid diseases, history of the disease, and a history of previous PCR testing. Occupational Safety and Health Department of the University of Indonesia Hospital conducted contact tracing for the patients or hospital staff

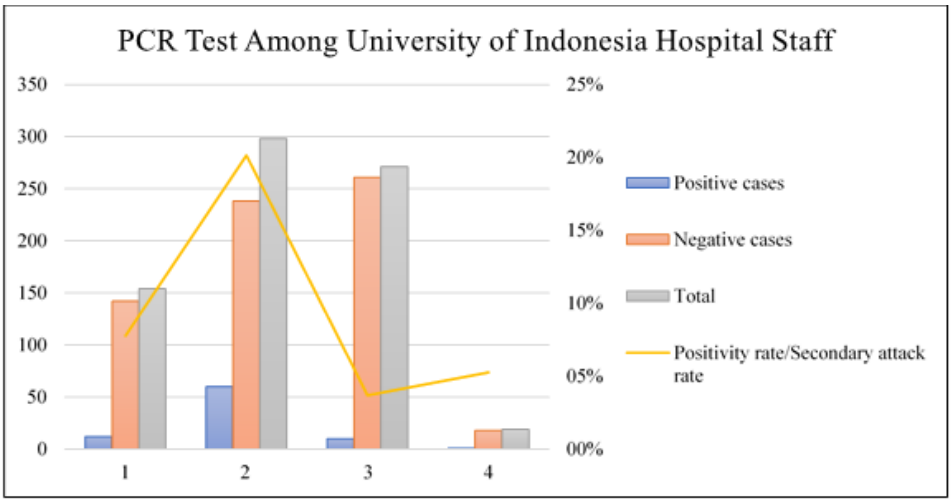
with a positive PCR test result. Individuals who had contact with a COVID-19 case were tested by PCR. If the PCR test results are positive, the patient must be isolated. This isolation could be performed at a hospital or self-isolation at home.

Tracing is carried out based on three levels of contact tracing, namely high risk, medium risk and low risk. Included in the high risk criteria are people who have had direct contact with a positive COVID-19 patient with a distance of less than one meter, more than fifteen minutes, without using personal protective equipment, or using inadequate personal protective equipment. The medium risk category is people who have direct contact with patients under surveillance who have not been confirmed positive for COVID-19 with a distance of less than one meter, more than fifteen minutes, without using personal protective equipment, or using inadequate personal protective equipment. Meanwhile, the low risk category is people who have direct contact with patients under surveillance or people under surveillance who have not been confirmed positive for COVID-19 with a distance of less than one meter, more than fifteen minutes, using personal protective equipment according to standards. For people in the high risk category, a swab test will be carried out the following day. It is attempted to finish the results of the swab on the same day to determine the next tracing.

RESULTS

PCR testing was performed for 742 hospital staff members consisting of 154 staff members in the testing phase and 557 in the tracing phase (**Figure 1**). Of all PCR tests, 83 staff members tested positive for COVID-19 (11.1%). The Occupational Health and Safety, Department of the Universitas Indonesia Hospital traced staff members who tested positive. The criterion for identification of close contact was: close contact with COVID-19 confirmed patient within 2 meters for a minimum of 15 minutes. Those who were found positive were advised to isolate themselves. The staff could choose between self-isolation and hospital isolation, and participants who self-isolated at home were asked to fill out the monitoring form.

Figure 1 shows the decline of positive cases found using PCR tests performed at the



	Testing	Tracing 1	Tracing 2	Tracing 3
Positive cases	12	60	10	1
Negative cases	142	238	261	18
Total	154	298	271	19
Positivity rate/Secondary attack rate	7.8%	20.1%	3.7%	5.3%
Trace per case		1:24	1:4	1:2

Figure 1. PCR test results among Universitas Indonesia Hospital staff.

Table 1. Demographic data of PCR test in the Universitas Indonesia Hospital

Variables		Positive (%)	Negative (%)	Total	Attack Rate (%) (CI 95%)	P value
Age	- <30 years	5 (41.7)	93 (62.8)	98	5 (0.01-0.09)	0.122*
	- ≥30 years	7 (58.3)	49 (34.5)	56	13 (0.04-0.22)	
Sex	- Male	4 (33.3)	47 (33.1)	51	8 (0.01-0.15)	1.000*
	- Female	8 (66.7)	95 (66.9)	103	8 (0.03-0.13)	
Occupation	Health worker	4 (33.3)	19 (13.4)	23	17 (0.02-0.32)	0.083*
	- Doctor	2 (16.7)	10 (7.0)	12		
	- Nurse	1 (8.3)	9 (6.3)	10		
	- Midwife	1 (8.3)	0 (0)	1		
	Non health worker	8 (66.7)	123 (86.6)	131	6 (0.02-0.10)	

University of Indonesia Hospital. The positivity rate of the PCR test in the testing phase was 7,8% (confidence interval [CI] 95%; 0,04−0,12). The secondary attack rate was the number of cases that occurred among close contacts who were traced. Secondary attack rate among hospital staff from tracing one declined with time, 20.1% (CI 95%; 0.15−0.25) to 3.7% (CI 95%; 0.02−0.06) and 5.3% (CI 95%; -0,05−0,15). The secondary attack rate of all 588 close contacts was 12.1% (CI 95%; 0,09−0,15) (71 cases per 588 close contacts). It was higher than the attack rate found in the testing phase (12,1% vs. 7,8%).

Testing

Detection of COVID-19 infection among the staff of the University of Indonesia Hospital was achieved using a PCR test for 154 members (health workers and non-health workers), who were routinely tested. Health workers consisted of doctors and nurses. Data regarding demographic characteristics of the PCR test are presented in **Table 1**. Statistical analysis showed no significant associations among variables (p >0.05).

Tracing

Tracing was carried out for confirmed COVID-19 positive cases by monitoring their interactions with families or colleagues. The confirmed positive staff filled in the contact history form and reported their condition to their manager and Occupational Health and Safety team. Furthermore, the close contacts of the confirmed positive cases were tested by PCR. If the contacts were found positive, tracing would continue until there were no positive cases left at the University of Indonesia Hospital.

Tracing were done 3 times, namely tracing 1, 2 and 3. Starting with 12 positive cases in the testing phase, 298 PCR tests were performed for their close contacts (clusters); thus, the trace per case ratio was 1:24 (tracing 1). From 298 cases, 60 new positive cases were detected (positivity rate 20,1%) and were retraced to find 271 new close contacts (case per trace ratio 1:4) in tracing 2. From 271 cases, 10 new positive cases were found and retraced (positivity rate 3.7%). The last, 19 close contacts were identified from previous cases (1:2) and we successfully detected only 1 new positive case in tracing 3 (positivity rate 5.3%).

The infection rate of health workers from the testing phase to tracing increased compared to that of non-health workers (7 vs. 5 times), although the secondary attack rate in health workers was lower than that in non-health workers (10.5% vs. 13.5%). We found a statistically significant association between age and PCR results, but found no similar results in other variables (**Table 2**).

Treatment

Positive cases of COVID-19 among the staff of the University of Indonesia Hospital were isolated or quarantined to stop the spread of the infection. Comfort and psychological reassurance were provided for the patients and the people surrounding them. The University of Indonesia Hospital provided two options for isolation: hospital isolation or self-isolation at home. Self-isolation was for two weeks, whereas in hospital isolation, patients could be discharged after they consecutively tested negative twice

Table 2. Demographic data of tracing phase

Variables	Tracing 1 (n)		Tracing 2 (n)		Tracing 3 (n)		Total (n)		P value	Secondary attack rate (%)	95% CI
	+	-	+	-	+	-	+	-			
Age											
- <30 year	36	141	6	218	0	17	42	376	0.018*	10.0	0.07-0.13
- > 30 year	24	97	4	43	1	1	29	141		17.1	0.11-0.23
Sex											
- Male	23	94	4	78	0	9	27	181	0.618*	13.0	0.08-0.18
- Female	37	144	6	183	1	9	44	336		11.6	0.08-0.15
Occupation											
- Health Worker	22	82	8	161	0	12	30	255	0.264*	10.5	0.07-0.14
- Non-	38	156	2	100	1	6	41	262		13.5	0.10-0.17
Total (n)	60	238	10	261	1	18	71	517		12.1	0.09-0.15

*Statistical analysis using Chi-square test

Table 3. Age, length of stay and duration of conversion.

	Mean (SD)	Min	Max
Age (n=83), year	29.4 (7.4)	19	57
Length of stay (n=44), day	8.7 (3.59)	3	25
Duration of conversion (n=82), day	12.0 (4.00)	3	28
- Self-isolation (n=39), day	13.8 (4.23)	7	28
- Hospital isolation (n=43), day	10.41 (2.99)	6	19

Table 4. Association of age, isolation types, and duration of conversion

Variables	Duration of conversion (n=82)		P value
	<14 days	≥14 days	
Isolation			
- Self-isolation	18 (32.1)	21 (53.8)	0.000*
- Hospital isolation	38 (67.9)	5 (19.2)	
Age			
- <30 years	35 (62.5)	11 (42.3)	0.086*
- ≥ 30 years	21 (37.5)	15 (57.7)	

*Statistical analysis using Chi-square test

by PCR, and were declared as fit to work by an occupational doctor. During isolation, staff could do their work from home by complying with health protocols.

Of the 83 positive staff members, 44 stayed at the hospital for isolation, and 39 were isolated at home. The average length of stay for hospital isolation was 8 days, with 25 as the longest. Ages of the staff members ranged from 19 to 57 years, with an average age of 29 years (**Table 3**). The average duration for the PCR test to become negative in two consecutive tests was 12 days. One staff member hospitalized at the Universitas Indonesia Hospital have not reached negative conversion leading to exclusion from the study. **Table 4** shows the association between conversion duration and type of isolation and age. The type of isolation was correlated with the duration of conversion.

Besides isolation, there were several measures to control infection in the hospital cluster. This was done by implementing a special protocol related to COVID-19; using appropriate self-protection equipment for those who had direct contact with COVID-19 patients, obligatory mask for all staff in the hospital, body temperature checking, promoting hand hygiene by providing hand sanitizer and soap supply, management of the working area by limiting the number of staff members in one room, physical distancing, and ensuring healthy air circulation.

DISCUSSION

Prevention of the spread of infection is a major goal in controlling COVID-19. The WHO has recommended the identification of cases, contact tracing, and isolation for individuals

with COVID-19. One strategy that can be used to prevent the spread is the 3T (test, trace, and treatment) strategy, which has proven to be able to control COVID-19 outbreaks in several countries, such as South Korea, Singapore, and Scotland.[9] The implementation of the 3T strategy in Scotland started with PCR testing on patients, health workers, and social workers. If a positive test result was found on examination, tracing would be carried out by the National Contact Tracing Service to identify those who had close contact with the confirmed case, including everyone who had a contact history of being within 2 meters for 15 minutes or more. People who had close contact with confirmed cases were contacted by the National Contact Tracing Service to identify the symptoms and advised to self-isolate for 14 days if they were asymptomatic. However, if the person showed symptoms of COVID-19, then tracing would continue to identify a history of close contact with that person.[10] Moreover, tracing conducted in South Korea and Singapore was also through the GPS on cell phones, transaction history, and CCTV recordings in public areas.[9]

COVID-19 testing should be done in all the hospital staff, and not only limited to the public. A report by Imperial College London states that routine weekly PCR tests can identify asymptomatic or mild symptom cases and become the basis for tracing people who have close contact with the confirmed cases.[11] Routine PCR testing of health workers and risk groups helped to reduce the rate of virus transmission by 25%-33%, higher than isolation alone.[12] Contact tracing should be done by considering the individual-level variation in transmission. The higher the transmission variation, the more people will have to undergo an examination. The WHO has recommended that 10-30 examinations should be performed for each confirmed case. Indonesia has also implemented this recommendation by conducting 20-30 examinations in the confirmed cases. This tracking has been implemented in several cities in Indonesia, such as DKI Jakarta and Surabaya.

The Depok government has set 3600 PCR tests dedicated to examining health workers in Depok, including the University of Indonesia Hospital.[11] Therefore, as referral hospitals of COVID-19 in Depok, the University of Indonesia Hospital conducted a mass PCR test for the staff, followed by tracing and isolation to ensure safety from COVID-19 infection. PCR test from mass swab test found 12 positive cases from 154 people (7.8%). Because of that, contact tracing was carried out and resulted in the hospital having to do more swab tests with a ratio of 1:24 (out of 12 positive cases, the next swab test was 298). From 298 people, 60 (20.1%) were confirmed cases which later resulted in more contact tracing. Then for second tracing from 60 positive cases resulted in 271 contact tracing with a trace per case ratio 1: 4 and found 10 positive cases (3.7%). From 10 positive cases, the third contact trace to 19 people and only found 1 positive case. All test conducted by the University of Indonesia Hospital was able to detect 83 (11.2%) confirmed cases from four examination periods and a total of 742 staff examined, namely the testing phase, tracing 1, tracing 2, and tracing 3. Tracing of close contact from the first 12 cases in the testing phase was able to detect 60 new cases with a trace per case ratio of 1:24. In the next tracing, new case findings decreased to 1 new case per 4 close contacts and 3rd trace was 1:2. The ratio reduction indicates that the need for tracing will be higher in the first tracing cluster and lower if the cluster has been treated. When compared to mass swab tests, the result of first tracing shows the important role of tracing over mass swabs, 20.1% compared to 7.8 % (positivity rate of mass swab test) or 12.3% (positivity rate of Indonesia in July 25, 2020). This shows a positive rate of contact tracing almost three times than a mass swab (20.1% compared to 7.8%). This percentage is higher than that observed in China where the infection rate of the hospital staff was 1.1%.[5] Focusing on contact tracing is crucial in Indonesia, where financial condition and PCR test price are not favorable. In the future, mass swabs are not specifically required, and if they are done, they should be done based on cluster sampling followed by tracing. Because mass PCR tests conducted on 5% of the population per week were estimated to reduce transmission by 2%.[13] Meanwhile from tracing we can conduct until 12% of the population. The higher number

of cases in the University of Indonesia Hospital could be caused by close contact between staff and confirmed cases.

The staff members of the University of Indonesia Hospital with positive results on the PCR test were asked to isolate. The implementation of the tracing and isolation strategies can reduce transmission of COVID-19 (47%-64%) better than isolation strategies alone (29-37%).[13] According to the WHO guidelines, confirmed and suspected cases must be isolated in health facilities to prevent the spread of coronavirus. If the number of health facilities is inadequate, isolation is prioritized for individuals with poor prognosis, such as aged >60 years and having a comorbid disease. Patients with mild or asymptomatic symptoms can self-isolate at home or other non-health facilities, such as hotels or stadiums, by implementing standard health precautions.[14] The Indonesian Ministry of Health has also established guidelines for patients undergoing independent isolation: the patient is placed in a separate room that is well ventilated; both patients and families caring for patients will use masks; patient will restrict movement and sharing the same room with family members; patient will use separate cutlery; patient will sleep separately from family members or use a different bed; one healthy caretaker will take care of the patient; family members must wash their hands after every contact with the patient or the patient's environment. Patients undergoing self-isolation need daily monitoring, including identification of symptoms, such as fever, colds, sore throat, shortness of breath, and other complaints, such as mental health and psychosocial support.[15]

The University of Indonesia Hospital chose hospital isolation because it can reduce risk community transmission even though it involves a higher cost than self-isolation. About 42% of staff infected with COVID-19 chose to self-isolate at home, whereas others chose hospital isolation. 21 patients (53.8%) who did self-isolation at home converted swab test result in more than 14 days, the remaining 18 patients (32.1%) converted in less than 14 days. Meanwhile, 38 patients (67.9%) isolated in hospital converted in less than 14 days. Five patients (19.2%) who were isolated in hospital converted in more than 14 days. A significant difference in the conversion time (less than 14 days and more than 14 days) from the staff was in self-isolation and hospital isolation. Hospital isolation can also reduce the stigma of COVID-19 infection. Social stigma and discrimination can been experienced by infected patients, their families, health workers, and other frontline officers who have treated COVID-19 patients. Thus, it is important to consider socio-psychological impacts, such as stigma and discrimination in each phase of the COVID-19 emergency response. Reasonable attention must be given to assist in the integration of people affected by COVID-19.[16]

This study found that the infection rate in health workers was lower than that in non-health workers. Lai, et al.[5] also found a similar result in a study, where infection rates among front-liner hospital staff were lower than in the non-front liners. Many factors may lead to lower infection rates, such as self-protection, equipment availability, usage, and compliance with health precaution protocols.

CONCLUSION

Test, trace, and treatment (3T) strategy is a strategy to eliminate the spread of COVID-19 in the hospital environment. This strategy could be used to control COVID-19 infection because the infection rate of the hospital staff was quite high (11%). Case identification of COVID-19 should be followed by contact tracing. In one confirmed case, 24 additional tests were needed. The staff members who were confirmed positive were isolated. The random test is still applied but the sample does not need to include all staff due to the high cost. We recommend samples to be taken on a random basis per-unit or per-profession. From this randomized test, if some positive people are found, contact tracing is necessary. PCR test results must be obtained within 24 hours, so that people who are being tracked are not isolated for too long while waiting for the results and services at the hospital do not have to be closed. Tracing was carried out until positive COVID-19 results were no longer found. 3T strategy implementation should be performed simultaneously with other health protocols to

reduce the risk of infection spreading, such as hand hygiene, physical distancing, and working space management.

REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
2. WHO. WHO Coronavirus Disease (COVID-19) dashboard. 2020;Available from: https://covid19.who.int/.
3. COVID-19 GTPP. Peta sebaran | Gugus Tugas Percepatan Penanganan COVID-19 [Internet]. covid19.go.id [cited 2020 Jul 20]; Available from: https://covid19.go.id/peta-sebaran.
4. Kota Depok I Covid-19 [Internet]. [cited 2020 Jul 20];Available from: https://ccc-19.depok.go.id/.
5. Lai X, Wang M, Qin C, et al. Coronavirus disease 2019 (COVID-2019) infection among health care workers and implications for prevention measures in a tertiary hospital in Wuhan, China. JAMA Netw Open 2020;3:e209666.
6. Safutra I. 75 Tenaga kesehatan di Jatim positif Korona [Internet]. 2020 [cited 2020 Jul 14];Available from: https://www.jawapos.com/surabaya/20/06/2020/75-tenaga-kesehatan-di-jatim-positif-korona/.
7. Yandiputra AR. Perawat positif Corona, RSUD Depok tutup sementara - Metro Tempo.co [Internet]. 2020 [cited 2020 Jul 16];Available from: https://metro.tempo.co/read/1345168/perawat-positif-corona-rsud-depok-tutup-sementara.
8. Testing, tracing, and when to lift restrictions: WHO's latest advice [Internet]. UN News2020 [cited 2020 Jul 20];Available from: https://news.un.org/en/story/2020/04/1061642.
9. Lucy H. Testing for COVID-19: A way to lift confinement restrictions. 2020;21.
10. Scottish Government. Covid-19 – Test, trace, isolate, support: A public health approach to maintaining low levels of community transmission of COVID-19 in Scotland. 2020.
11. Rivett L, Sridhar S, Sparkes D, et al. Screening of healthcare workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission. eLife 2020;9:e58728.
12. Grassly N, Pons Salort M, Parker E, et al. Report 16: Role of testing in COVID-19 control [Internet]. Imperial College London; 2020 [cited 2020 Jul 14]. Available from: http://spiral.imperial.ac.uk/handle/10044/1/78439
13. Kucharski AJ, Klepac P, Conlan AJK, 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. Lancet Infect Dis [Internet] 2020 [cited 2020 Jul 16];0. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30457-6/abstract.
14. World Health Organization. Considerations in the investigation of cases and clusters of COVID-19: interim guidance [Internet]. 2020 [cited 2020 Jul 14];Available from: https://apps.who.int/iris/handle/10665/331668.
15. Kementerian Kesehatan Republik Indonesia. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/MENKES/413/2020 Tentang Pedoman Pencegahan dan Pengendalian Coronavirus Disease 2019 (COVID-19).
16. Inter-Agency Standing Committee. Catatan tentang aspek kesehatan jiwa dan psikososial wabah COVID-19 Versi 1.0 [Internet]. Available from: https://www.who.int/docs/default-source/searo/indonesia/covid19/catatan-tentang-aspek-kesehatan-jiwa-dan-psikososial-wabah-covid-19-feb-2020-indonesian.pdf?sfvrsn=ebae5645_2.

Factors Related to Knowledge, Perception, and Practices Towards COVID-19 Among Patients with Autoimmune Diseases: A Multicenter Online Survey

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ABSTRAK

Latar belakang: *penyintas autoimun lebih rentan untuk mengalami infeksi. Pengetahuan yang cukup, persepsi dan perilaku yang baik sehubungan dengan COVID-19 penting untuk penyintas autoimun selama pandemi. Studi ini bertujuan untuk mengetahui tingkat pengetahuan, persepsi dan perilaku penyintas autoimun terkait pandemi COVID-19.* ***Metode:*** *studi potong lintang menggunakan survei daring dilakukan dari April sampai Mei 2020. Penyintas autoimun ditanyakan mengenai karakteristik demografi, diagnosis, riwayat pengobatan, pengetahuan, persepsi dan perilaku terkait COVID-19.* ***Hasil:*** *total responden sebanyak 685 orang. Mayoritas adalah perempuan, memiliki diagnosis lupus eritematosus sistemik, dengan median usia 37 tahun. Hampir semua responden memiliki pengetahuan yang baik terkait penularan COVID-19 dan melakukan perilaku yang tepat. Kecukupan informasi dan penggunaan steroid atau mofetil mikofenolat/asam mikofenolat (MMF/MPA) berhubungan dengan persepsi bahwa pandemi memengaruhi kesehatan mereka. Kunjungan ke klinik swasta dan penggunaan hidroksiklorokuin/klorokuin atau sulfasalazin berhubungan dengan persepsi penyakit autoimun dapat menyebabkan penyintas autoimun lebih rentan terinfeksi COVID-19. Penyintas autoimun yang bekerja dari rumah berhubungan dengan*

persepsi bahwa ketika terinfeksi COVID-19, gejala yang timbul lebih berat. Berdomisili di daerah Sumatera dan mendapatkan hidroksiklorokuin/klorokuin sulfat atau MMF/MPA berhubungan dengan persepsi bahwa pengobatan autoimun dapat mengurangi risiko terinfeksi COVID-19. Kecukupan informasi, pendidikan universitas, kunjungan ke klinik swasta dan penggunaan hidroksiklorokuin/klorokuin sulfat berhubungan dengan persepsi bahwa pandemi COVID-19 akan menyebabkan penyintas semakin sulit mendapatkan obat. ***Kesimpulan:*** *hampir semua responden memiliki pengetahuan yang baik dan melakukan kebiasaan yang tepat terkait COVID-19. Kecukupan informasi, jenis pengobatan autoimun, bekerja dari rumah, latar belakang pendidikan, domisili tempat tinggal, dan fasilitas kesehatan berhubungan dengan persepsi penyintas autoimun terkait pandemi COVID-19.*

Kata kunci: *pengetahuan, persepsi, perilaku, autoimun, COVID-19.*

ABSTRACT

Background: *autoimmune patients can be more susceptible to infection. Proper knowledge, perception, and practices towards COVID-19 are essential for these patients during pandemic. This study aimed to know their knowledge, perception, and practices regarding COVID-19.* ***Methods:*** *cross sectional study using online survey was conducted from April to May 2020. Patients with autoimmune disease were asked about demographic characteristics, diagnosis, history of treatment, knowledge, perception, and practice regarding COVID-19.* ***Results:*** *there were 685 respondents. Most of them were female and had systemic lupus erythematosus with median age of 37 years old. Almost all respondents had good knowledge regarding transmission of COVID-19 and did proper prevention practices. Adequacy of information and steroid or mycophenolate mofetil/mycophenolic acid (MMF/MPA) use were related to perception of the effect of pandemic to their own health. Visiting private clinic and receiving hydroxychloroquine/chloroquine sulfate or sulfasalazine were related to perception that autoimmune conditions would make them more prone to COVID-19. Work from home was related to perception that when contracting COVID-19, the symptoms would be more severe. Living in Sumatra region and getting hydroxychloroquine/chloroquine sulfate or MMF/MPA were related to perception that autoimmune medications could reduce risk of getting COVID-19. Adequate information, university education, private clinic visit, and hydroxychloroquine/chloroquine sulfate use were related to perception that COVID-19 pandemic would cause difficulties in getting medications.* ***Conclusion:*** *almost all respondents had good knowledge and practices regarding COVID-19. Adequacy of information, autoimmune treatment, work from home, educational background, area of living, and health care facilities contributed to perception regarding COVID-19 pandemic.*

Keywords: *knowledge, perception, practice, autoimmune, COVID-19.*

INTRODUCTION

On March 11, World Health Organization declared COVID-19, an infection caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), as a pandemic outbreak.[1] The number of confirmed cases as of 25 June 2020 was more than eight million cases, while the number of deaths reached 479,133 cases.[2]

Pre-existing impaired immune response can likely contribute to the immunopathogenesis of COVID-19.[3] Autoimmune disease occurs when immune system attacks the body own cells. To control the disease activity, some patients with autoimmune diseases need immunosuppressant. These conditions make them more susceptible to infection.[4,5] Therefore, during this pandemic, there are concerns among patients with autoimmune diseases whether they will be more prone to get COVID-19 infection or not and the greater risk of presenting a severe form of COVID-19 infection. However, there is still not enough evidence to answer these questions.

Knowledge and perception towards COVID-19 pandemic are essential for patients with autoimmune diseases. In the absence of effective COVID-19 treatment, the implementation of protective measures will potentially prevent the people from getting infected by the disease and reduce disease dissemination.[6] They should obtain accurate

information about COVID-19 and how to prevent the disease and practice the preventive measures properly. To improve the management of autoimmune patients in Indonesia during this COVID-19 pandemic, it is important to know about their knowledge, perception, and practices regarding COVID-19 pandemic.

METHODS

We conducted a cross-sectional study using online survey in Indonesian language from April to May 2020. Inclusion criterion was patients diagnosed with autoimmune disease, and the exclusion criterion was those who refused to participate. People that fulfilled the criteria would be included in the study. The required sample was the total sampling from the filled online survey. This study had been approved by Ethical Committee of Faculty of Medicine Universitas Indonesia (KET-443/UN2.F1/ETIK/PPM.00.02/2020).

Data Collection

We developed and published an online survey for patients with autoimmune diseases through foundations or patient support group. The survey was disseminated to 23 Whatsapp and Facebook groups which had 3588 members. A patient can be a member of different groups. Respondents were given informed consent and if they agreed, then they filled out the survey. The questions were developed to get information about demographic characteristics of the respondents, diagnosis, history of treatment, and the respondents' knowledge, perception, and practices regarding COVID-19 pandemic and their health. Six hundred eighty-eight respondents joined the online survey. Three respondents were not included in analysis because did not give proper autoimmune diagnosis.

Statistical Analysis

Statistical analysis relied on Microsoft Excel and SPSS version 20.0. Bivariate analysis of two categorical data was conducted with Chi Square. Multivariate analysis was conducted with logistic regression.

RESULTS

A total of 685 patients with autoimmune diseases joined the online survey. Most of the respondents were female (637 subjects; 93%) with median age of 37 (IQR 29-45) years old. All but two respondents lived in Indonesia (**Figure 1**). Most respondents (84.5%) lived in Java Island.

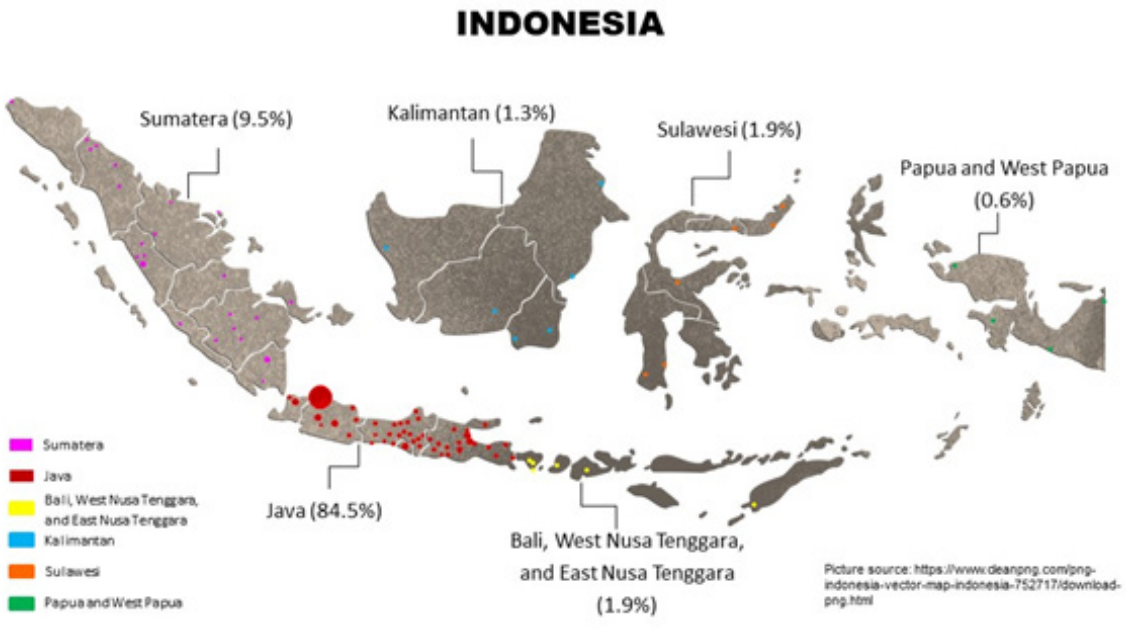

Figure 1. Distribution of respondent's residence location.

Table 1. Characteristics of study subjects

Characteristics (N=685)	Number (%)
Age group	
- <19 years old	14 (1.9)
- 19-60 years old	654 (95.7)
- >60 years old	17 (2.4)
Educational background	
- Basic (elementary and junior high school)	16 (2.3)
- Intermediate (senior high school)	160 (23.4)
- High (university)	506 (73.9)
- No data	3 (0.4)
Occupation	
- Health care worker	34 (5)
- Non-health care worker	416 (60.7)
- Not working	232 (33.9)
- No data	3 (0.4)
Health Funding	
- National insurance program	447 (65.3)
- Other insurance	82 (12)
- Other funding	120 (17.5)
- Self-funding	288 (42)
Health care facilities	
- Government hospital	373 (54.5)
- Private hospital	384 (56.1)
- Public Health Center (*Puskesmas*)	85 (12.4)
- Private clinic	109 (15.9)
Diagnosis of autoimmune diseases	
- Systemic lupus erythematosus	277 (40.4)
- Sjogren's syndrome	140 (20.4)
- Rheumatoid arthritis	131 (19.1)
- Psoriasis	86 (12.6)
- Autoimmune thyroid disease	44 (6.4)
- Antiphospholipid syndrome	36 (5.3)
- Vasculitis	31 (4.5)
- Inflammatory bowel disease	25 (3.6)
- Immune Thrombocytopenia Purpura	24 (3.5)
- Myositis	20 (2.9)
- Autoimmune hemolytic anemia	15 (2.2)
- Myasthenia gravis	13 (1.9)
- Multiple sclerosis	11 (1.6)
- Ankylosing spondylitis	8 (1.2)
- Systemic sclerosis	7 (1)
- Uveitis	4 (0.6)
- Chronic Inflammatory demyelinating polyneuropathy	4 (0.6)
- Other autoimmune neurology (Guillain barre syndrome, neuromyelitis optics, transverse myelitis, multifocal motor neuropathy)	9 (1.3)
- Other autoimmune diseases (type 1 diabetes, celiac disease, alopecia areata, rheumatic fever, interstitial lung disease, autoimmune hepatitis, Evan's syndrome, pemphigus vulgaris, sarcoidosis, primary biliary cirrhosis, adult onset still disease, mixed connective tissue disease, juvenile rheumatoid arthritis, vitiligo)	32 (4.7)
Comorbidities	
- Allergy	149 (21.8)
- Hypertension	59 (8.6)
- Asthma	56 (8.2)
- Diabetes mellitus	16 (2.3)
- Pulmonary tuberculosis	15 (2.2)
- Heart diseases	15 (2.2)
- Cerebrovascular disease	8 (1.2)
- Renal failure	5 (0.7)
- Malignancies	3 (0.4)
- No comorbidities	306 (44.7)

Table 1. Characteristics of study subjects

Characteristics (N=685)	Number (%)
Medications	
Steroid use	
- No steroid	293 (42.8)
- <7.5 mg per day equivalent prednisone	260 (38)
- 7.5 mg-30 mg per day equivalent prednisone	116 (16.9)
- >30 mg per day equivalent prednisone	13 (1.9)
- No information	3 (0.4)
Steroid sparing agent	
- Hydroxychloroquine/Chloroquine sulfate	181 (26.4)
- Mycophenolate mofetil/mycophenolic acid	153 (22.3)
- Methotrexate	90 (13.1)
- Azathioprine	50 (7.3)
- Sulfasalazine	36 (5.3)
- Cyclosporine	24 (3.5)
- Mesalamine	18 (2.6)
- Leflunomide	10 (1.5)
- Tacrolimus	7 (1)
- Cyclophosphamide	6 (0.9)
- Biologics	5 (0.7)
- Budesonide	2 (0.3)
- Acitretin	1 (0.1)

Table 1 shows other characteristics of study subjects. More than half of the subjects got treatment at government hospital and used national insurance program. Most respondents had high educational background, were diagnosed with systemic lupus erythematous, and had no comorbidities. Almost half of respondents did not get any steroid (42.8%). Mycophenolate mofetil or mycophenolic acid and hydroxychloroquine/ chloroquine sulphate were steroid sparing agent that was used the most.

Source of Information Related to COVID-19 Pandemic

Figure 2a shows sources from where respondents got COVID-19 information. Television was the main source of information of COVID-19 (66%), followed by doctor/medical staff (43%). More than a quarter of respondents got information from social media: Whatsapp/ Line/Telegram (38%) and Instagram (29%).

Ninety-one subjects (13.3%) said that they did not get enough information related

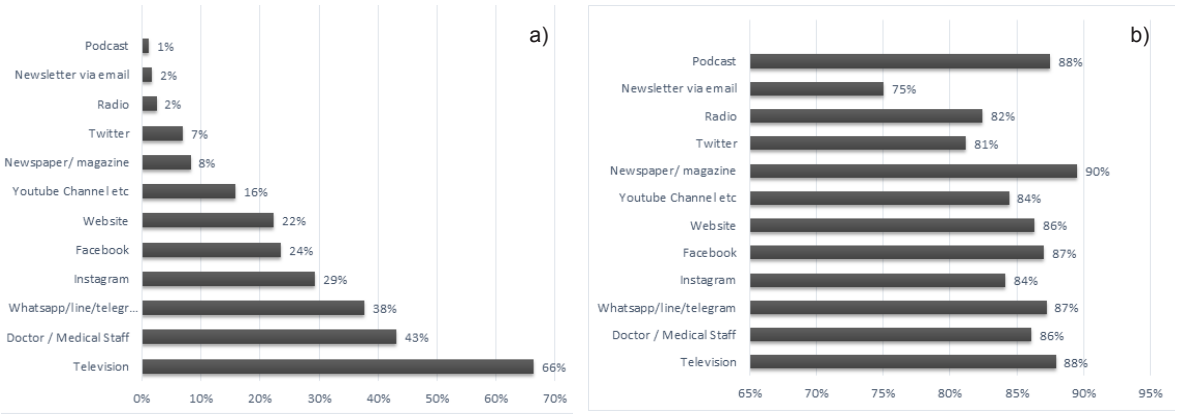

Figure 2. Sources of COVID-19 information (a) and respondent's satisfaction for each source of information (b).

to COVID-19 pandemic. Satisfaction for each resource of information is shown in **Figure 2b**. Information from newspaper or magazine was the most satisfying source (90%), higher than information from doctor or medical staff (86%).

Knowledge, Perception, and Practice of Study Subjects Related to COVID-19 Pandemic

About 670 respondents (97.8%) gave right answers on how COVID-19 infection could be transmitted (via droplet), seven respondents (1%) gave wrong answers and eight respondents (1.2%) answered that they did not know how it could be transmitted. No respondents who used podcast, newsletter, or radio as sources of information gave wrong answers (**Table 2**). The proportion of respondents giving right answer was similar according to adequacy of information and educational background.

Some questions were related to subject's perception on the effect of COVID-19 pandemic to their own health. Most of the respondents (79.7%) felt anxious but that did not affect their daily life. The others feel worried and that affected their daily activities (15.3%), but others did not feel worried (5%). Most of respondents thought that they were more prone to COVID 19 infection (587 subjects, 85.7%) and would be more severe if getting COVID-19 infection (359 subjects; 52.4%). About 148 (21.6%) respondents thought that their medications could reduce their risk of getting COVID-19 infection. Half of the respondents (344 subjects; 50.2%) were afraid that the pandemic would cause difficulties in getting their medications.

We did analysis to know factors related to respondent's perceptions during COVID-19 pandemic. **Table 3** shows results of bivariate and multivariate analysis of patients' variable with perception. On perception of the effect of pandemic to their own health, adequate COVID-19 information and steroid use were related to lower risk of feeling worried which affected their daily activities (p=0.02; OR 0.09 95% CI 0.01-0.72 and p=0.01; OR 0.29 95% CI 0.11-0.76, respectively). Higher risk was seen in respondents who got MMF/MPA (p=0.01;

Table 2. Knowledge on COVID-19 transmission.

Variables	COVID-19 transmission	
	Right answer 670 respondents (%)	Wrong answer/did not know the answer 15 respondents (%)
Source of information		
Doctor or other health professionals	286 (96.9)	9 (3.1)
Television	446 (98)	9 (2)
Whatsapp/Line/Telegram platform	256 (99.2)	2 (0.8)
Instagram	194 (96.5)	7 (3.5)
Facebook	160 (99.4)	1 (0.6)
Website	152 (99.3)	1 (0.7)
Youtube	107 (98.2)	2 (1.8)
Newspaper/magazine	56 (98.2)	1 (1.8)
Twitter	46 (95.8)	2 (4.2)
Radio	17 (100)	0 (0)
Newsletter	12 (100)	0 (0)
Podcast	8 (100)	0 (0)
Adequacy of information related to COVID-19		
Adequate	581 (97.8)	13 (2.2)
Not adequate	89 (97.8)	2 (2.2)
Educational background		
Elementary school & junior high school (16 respondents)	15 (93.8)	1 (6.2)
Senior high school & universities (666 respondents)	652 (97.9)	14 (2.1)
No information (3 respondents; 0.4%)	3 (100)	0 (0)

Table 3. Bivariate and multivariate analysis of patient's variable to perception related to COVID-19 pandemic

Patient's variables	How does this COVID-19 pandemic affect your health?																			
	Worried, affecting daily activities vs no worries (N=105 vs 34)				Anxious, but not affecting their daily life vs no worries (N=546 vs 34)				Autoimmune conditions would make patients more prone to COVID-19 infection (N=685)				When contracting COVID-19 infection, the symptoms would be more severe due to the autoimmune conditions (n=390)				Autoimmune medications could reduce the patients' risk of getting COVID-19 infection(N=546)				COVID-19 pandemic would cause difficulties in getting medications (N=546)			
	Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Female gender	0.32 (0.04-2.65)	0.45			0.40 (0.05-3.04)	0.72			1.88 (0.92-3.82)	0.08	1.84 (0.87-3.88)	0.11	1.39 (0.30-6.30)	0.66			1.45 (0.58-3.64)	0.42			0.52 (0.22-1.25)	0.14	0.47 (0.19-1.16)	0.10
Adequate inform. related to COVID-19	0.10 (0.01-0.79)	0.01	0.09 (0.01-0.72)	0.02	0.22 (0.03-1.64)	0.16	0.19 (0.02-1.41)	0.10	1.22 (0.67-2.22)	0.52			0.75 (0.22-2.56)	1			0.90 (0.51-1.57)	0.71			0.25 (0.13-0.50)	<0.001	0.22 (0.10-0.44)	<0.001
University education	0.89 (0.36-2.20)	0.80			0.88 (0.39-1.98)	0.75			1.06 (0.65-1.73)	0.81			1.30 (0.59-2.87)	0.51			0.86 (0.56-1.33)	0.50			0.56 (0.37-0.86)	0.01	0.60 (0.38-0.95)	0.03
National insurance program	0.92 (0.41-2.07)	0.85			1.05 (0.51-2.16)	0.90			1.29 (0.83-2.00)	0.26			1.11 (0.52-2.36)	0.78			1.22 (0.81-1.82)	0.35			1.05 (0.72-1.51)	0.81		
Other insurance	2.36 (0.28-19.88)	0.68			5.17 (0.70-38.4)	0.11		0.09	0.65 (0.36-1.18)	0.15	0.70 (0.38-1.32)	0.27	1.12 (0.38-3.33)	1			1.17 (0.67-2.04)	0.59			0.98 (0.58-1.67)	0.95		
Other funding	0.59 (0.22-1.62)	0.30			0.85 (0.36-2.02)	0.72			1.01 (0.58-1.78)	0.96			0.50 (0.22-1.20)	0.13	0.65 (0.23-1.88)	0.43	1.13 (0.69-1.87)	0.62			0.64 (0.40-1.01)	0.05	0.70 (0.42-1.18)	0.18
Self-funding	1.41 (0.64-3.12)	0.39			1.14 (0.56-2.33)	0.72	5.67 (0.76-42.37)		0.92 (0.60-1.41)	0.69			1.30 (0.61-2.80)	0.49			0.68 (0.46-1.00)	0.05	0.62 (0.16-2.39)	0.48	1.04 (0.73-1.48)	0.82		
Govern-ment hospital	1.62 (0.74-3.53)	0.22	2.37 (0.94-5.99)	0.07	1.32 (0.66-2.65)	0.43			1.42 (0.93-2.18)	0.12			1.63 (0.78-3.40)	0.19	1.03 (0.38-2.76)	0.95	0.97 (0.66-1.42)	0.86			1.40 (0.98-1.99)	0.06	1.04 (0.67-1.62)	0.87
Private hospital	0.64 (0.29-1.39)	0.26			0.95 (0.47-1.92)	0.88			0.82 (0.53-1.27)	0.37			0.65 (0.30-1.40)	0.27			1.08 (0.74-1.58)	0.68			0.65 (0.46-0.93)	0.02	0.69 (0.47-1.01)	0.06

Table 3. Bivariate and multivariate analysis of patient's variable to perception related to COVID-19 pandemic

Patient's variables	How does this COVID-19 pandemic affect your health?																			
	Worried, affecting daily activities vs no worries (N=105 vs 34)				Anxious, but not affecting their daily life vs no worries (N=546 vs 34)				Autoimmune conditions would make patients more prone to COVID-19 infection (N=685)				When contracting COVID-19 infection, the symptoms would be more severe due to the autoimmune conditions (n=390)				Autoimmune medications could reduce the patients' risk of getting COVID-19 infection(N=546)				COVID-19 pandemic would cause difficulties in getting medications (N=546)			
	Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Public health center	0.75 (0.24-2.30)	0.56			0.82 (0.31-2.20)	0.60			1.02 (0.53-1.95)	0.95			5.08 (0.68-38.07)	0.10	-	1	0.67 (0.35-1.27)	0.22	0.28 (0.04-1.82)	0.18	1.54 (0.86-2.74)	0.14	1.43 (0.77-2.64)	0.26
Private clinic	0.84 (0.30-2.35)	0.74			0.88 (0.36-2.20)	0.79			0.43 (0.26-0.70)	0.001	0.45 (0.26-0.78)	0.005	0.90 (0.33-2.45)	0.79			1.45 (0.87-2.43)	0.16	1.79 (0.48-6.63)	0.38	0.55 (0.34-0.90)	0.02	0.52 (0.31-0.88)	0.01
Sumatra vs other than Sumatra and Java	0.56 (0.08-3.80)	0.66			0.91 (0.16-5.29)	1			0.59 (0.15-2.39)	0.53			1.15 (0.18-7.53)	1			2.83 (1.04-7.71)	0.04	4.40 (1.29-14.94)	0.02	0.86 (0.33-2.25)	0.75		
Java vs other than Sumatra and Java	0.68 (0.14-3.31)	1			1.19 (0.27-5.24)	0.69			0.47 (0.14-1.56)	0.21	0.37 (0.12-1.25)	0.11	1.32 (0.29-6.01)	0.66			1.10 (0.46-2.64)	0.82			0.70 (0.31-1.56)	0.38		
Work from home	0.70 (0.22-2.18)	0.54			0.99 (0.35-2.79)	0.98			0.88 (0.49-1.60)	0.68			2.57 (1.06-6.26)	0.03	2.61 (1.06-6.45)	0.04	0.99 (0.58-1.70)	0.97			0.81 (0.50-1.33)	0.40		
Steroid	0.46 (0.20-1.05)	0.06	0.29 (0.11-0.76)	0.01	0.56 (0.26-1.19)	0.13	0.44 (0.20-0.96)	0.04	1.55 (1.01-2.38)	0.04	1.10 (0.67-1.81)	0.71	1.24 (0.50-2.60)	0.56			1.63 (1.06-2.49)	0.02	0.43 (0.08-2.24)	0.31	1.09 (0.76-1.58)	0.63		
Hydroxychloroquine/ chloro-quine sulfate	1.12 (0.45-2.78)	0.80			1.13 (0.50-2.56)	0.77			2.09 (1.17-3.73)	0.01	1.85 (1.02-3.36)	0.04	2.33 (0.79-6.82)	0.12	2.11 (0.58-7.63)	0.25	2.57 (1.73-3.81)	< 0.001	7.22 (2.23-23.38)	0.001	1.91 (1.29-2.84)	0.001	1.99 (1.32-3.01)	0.001
Azathioprine	0.63 (0.11-3.62)	0.63			1.40 (0.32-6.05)	1			1.24 (0.52-3)	0.63			0.91 (0.88-0.94)	0.10	-	1	0.94 (0.48-1.82)	0.85			0.79 (0.44-1.43)	0.44		
Mycophenolate mofetil mycophenolic acid	5.82 (1.31-25.88)	0.01	15.68 (1.93-127.31)	0.01	4.65 (1.10-19.69)	0.02	6.69 (1.55-28.80)	0.01	1.56 (0.88-2.76)	0.12	1.45 (0.78-2.70)	0.24	0.96 (0.42-2.23)	0.93			1.46 (0.97-2.19)	0.07	5.66 (1.86-17.23)	0.002	1.53 (1.02-2.29)	0.04	1.50 (0.98-2.30)	0.06

Table 3. Bivariate and multivariate analysis of patient's variable to perception related to COVID-19 pandemic

Patient's variables	How does this COVID-19 pandemic affect your health?																			
	Worried, affecting daily activities vs no worries (N=105 vs 34)				Anxious, but not affecting their daily life vs no worries (N=546 vs 34)				Autoimmune conditions would make patients more prone to COVID-19 infection (N=685)				When contracting COVID-19 infection, the symptoms would be more severe due to the autoimmune conditions (n=390)				Autoimmune medications could reduce the patients' risk of getting COVID-19 infection(N=546)				COVID-19 pandemic would cause difficulties in getting medications (N=546)			
	Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Cyclosporine	0.74 (0.67-0.82)	0.19	-	1	0.94 (0.92-0.96)	0.62			3.96 (0.53-29.63)	0.23	2.92 (0.38-22.70)	0.31	1.58 (0.20-12.28)	1			0.89 (0.35-2.29)	0.81			1.18 (0.50-2.82)	0.70		
Tacrolimus	0.75 (0.68-0.83)	1			0.94 (0.92-0.96)	1			0.86 (0.83-0.88)	0.60			0.92 (0.89-0.95)	1			2.04 (0.45-9.22)	0.40			1.48 (0.28-7.67)	1		
Methotrexate	0.54 (0.20-1.50)	0.26			0.57 (0.24-1.35)	0.19	0.73 (0.30-1.77)	0.48	1.58 (0.77-3.27)	0.21	1.71 (0.75-3.90)	0.20	0.76 (0.28-2.09)	0.58			0.91 (0.54-1.54)	0.73			0.93 (0.58-1.50)	0.77		
Cyclophospha-mide	0.24 (0.18-0.32)	0.24	-	1	0.30 (0.04-2.69)	0.30			0.33 (0.06-1.82)	0.21	0.16 (0.02-1.21)	0.08	0.34 (0.04-3.12)	0.34			1.35 (0.24-7.44)	0.66			2.96 (0.34-25.56)	0.42		
Sulfasalazine	0.97 (0.19-5.04)	1			0.86 (0.20-3.79)	0.69			6.15 (0.83-45.42)	0.04	8.94 (1.07-74.87)	0.04	1.58 (0.20-12.28)	1			1.44 (0.70-2.97)	0.32			0.99 (0.49-2.02)	0.98		
Mesalamine	0.75 (0.68-0.83)	1			0.94 (0.92-0.96)	1			2.89 (0.38-21.99)	0.49			1.22 (0.16-9.58)	1			0.57 (0.16-2.00)	0.58			0.51 (0.19-1.34)	0.17	0.36 (0.12-1.04)	0.06
Budesonide	-	-			0.94 (0.92-0.96)	1			0.86 (0.83-0.88)	1			0.92 (0.89-0.95)	1			0.73 (0.69-0.77)	1			0.63 (0.59-0.67)	0.53		
Leflunomide	-	-			0.94 (0.92-0.96)	1			0.38 (0.10-1.50)	0.16	0.38 (0.08-1.75)	0.21	0.17 (0.02-1.91)	0.22	0.28 (0.02-3.50)	0.32	0.33 (0.04-2.68)	0.46			1.18 (0.29-4.76)	1		
Biologics	0.75 (0.68-0.83)	1			0.94 (0.92-0.96)	1			0.25 (0.04-1.50)	0.15	0.40 (0.06-2.53)	0.33	0.08 (0.005-1.37)	0.15	0.08 (0.01-1.34)	0.08	0.73 (0.69-0.76)	0.58			0.19 (0.02-1.87)	0.15	0.49 (0.05-4.93)	0.54
Acitretin	-	-			0.94 (0.92-0.96)	1			0.86 (0.83-0.88)	1			0.92 (0.89-0.95)	1			0.73 (0.69-0.77)	1			0.63 (0.59-0.67)	1		

OR 15.68 95% CI 1.93-127.31). Use of steroid and MMF/MPA were also related to perception of anxious which did not affect daily activities (p=0.04; OR 0.44 95% CI 0.20-0.96 and p=0.01; OR 6.69 95% CI 1.55-28.80, respectively).

Respondents who went to private clinic were related to lower risk of having perception that autoimmune conditions would make them more prone to COVID-19 infection (p=0.005; OR 0.45 95% CI 0.26-0.78). On the other hand, hydroxychloroquine/chloroquine sulfate and sulfasalazine administration were related to perception (p=0.04; OR 1.85 95% CI 1.02-3.36 and p=0.04; OR 8.94 95% CI 1.07-74.87 respectively). Respondents who could work from home during COVID-19 pandemic were associated with higher risk of having perception that when contracting COVID-19 infection, the symptoms would be more severe due to the autoimmune conditions (p=0.04; OR 2.61 95% CI 1.06-6.45).

Respondents who lived in Sumatra region, got hydroxychloroquine/chloroquine sulfate, or got MMF/MPA showed higher risk of having perception that autoimmune medications could reduce their risk of getting COVID-19 infection (p=0.02; OR 4.40 95% CI 1.29-14.94, p=0.001; OR 7.22 95% CI 2.23-23.38; and p=0.002; OR 5.66 95% CI 1.86-17.23, respectively). Respondents with adequate COVID 19 information or university education or who visit private clinic had lower risk of having perception that COVID-19 pandemic would cause difficulties in getting medications (p<0.001, OR 0.22 95% CI 0.10-0.44; p=0.03, OR 0.60 95% CI 0.38-0.95; p=0.01 OR 0.52 (0.31-0.88) respectively). Respondents who got hydroxychloroquine/chloroquine sulfate showed higher risk of having that perception (p=0.001; OR 1.99 95% CI 1.32-3.01).

We also asked what respondents did as prevention to avoid contracting the infection as presented in **Table 4**. Washing hands, physical distancing, and wearing mask were the most common prevention practices. Interestingly, a small number of respondents said that they practiced spraying disinfectant to bodies, taking antibiotic, and using mouthwash to prevent COVID-19 infection. None of them used podcast nor came from lower educational background (elementary school up to junior high school).

From bivariate analysis, there was no significant relation between educational background and adequacy of information with wrong practices related to COVID-19 (p=1 and p=0.21 for spraying disinfectant to bodies; p=1 and p=1 for taking antibiotics; and p=1 and p=0.76 for using mouthwash).

Table 4. Practices to avoid getting COVID-19 infection.

Practices	Number (%)
Right practices	
- Washing hands	661 (96.5)
- Physical distancing	625 (91.2)
- Using face mask	615 (89.8)
- Staying at home	590 (86.1)
- Not touching face	565 (82.5)
- Consuming fruits or vegetables	490 (71.5)
- Getting adequate sleep	488 (71.2)
- Not using public transportation	442 (64.5)
- Disinfecting properties	400 (58.4)
- Taking supplements/multivitamins	351 (51.2)
- Sunbathing	289 (42.2)
- Exercising regularly	273 (39.9)
Wrong practices	
- Using mouthwash	25 (3.6)
- Spraying disinfectant to bodies	23 (3.4)
- Taking antibiotics	13 (1.9)

DISCUSSION

This study involved 685 autoimmune patients across Indonesia with mostly female respondents, median age of 37 years old and Java as their place of residence. Predominant finding of female gender was in accordance to the fact that women had higher incidence and prevalence of some specific autoimmune diseases than men did.[7] Most of our study participants were diagnosed with SLE (40.4%) and Sjogren's syndrome (20.4%) which were more commonly found among female. Most of our study participants (95.7%) were 19-60 years old. The onset age of autoimmune disease varied widely depending on the disease, but most commonly occurred between 15-55 years old.[8] Most of our participants lived on Java island (84.9%), which caused unequal distribution of

respondents. Several possibilities may explain this distribution, such as racial-genetic difference in Indonesian population and the difference of health care facilities capability across Indonesia for diagnosing autoimmune diseases.[9] Financial barrier in some Indonesian regions may lead to underdiagnosis of autoimmune diseases. Moreover, in some regions autoimmune laboratory tests were not readily available. The unequal distribution of Indonesian doctors may further contribute to lack of access for presumably autoimmune patients, with more than 57% of Indonesian doctors concentrated in Java-Bali.[10.11]

Most of our study participants were taking corticosteroid (57.2%) with low dosage (38%) to manage their autoimmune diseases. The use of low dose steroid might implicate that most of our participants were well controlled or had mild manifestation, therefore they could participate in our online survey.[12]

Individuals, organizations, and governments use social media to communicate with each other on a number of issues related to the COVID-19 pandemic.[13] COVID-19-related information can be taken from the following sources: the Internet, friends, traditional media, formal lessons on COVID-19 (whether online or in-person), medical staff in health care settings, coworkers, and family members.[14] The vast majority of the participants (86.7%) believed that they had enough information related to COVID-19 with leading main sources being television, doctor, and chatting application platforms. This finding might denote that television was the most accessible source of information for Indonesian citizens; therefore COVID-19 health campaign should be directed in television. Basch et al study[15] demonstrated the potential role of entertainment television in saving lives. The implication is that in addition to holding regular press briefings covered by national news, public health officials may be able to achieve our collective goal of community mitigation by appearing on other television programs and communicating clearly about the specific behaviors that people must practice to protect themselves, their families, and their communities.

Our study also shows that social media platforms and internet have become other leading sources of information compared to more conventional media platforms, such as newspaper. This finding may be explained by the fact that over 107.2 million people were predicted as internet user in Indonesia in 2019 and the relative young median age of our study participants.[16] Therefore, Indonesian government should utilize the social media more as the alternative source for COVID-19 education platform. However, social media can also be a source of misinformation, therefore monitoring by government is needed.

Knowledge is expected to largely influence the degree of adherence to the personal protective measures and ultimately the clinical outcome.[17] More than half of respondents had a good educational background, so that they were able to understand information better about COVID-19. Most of our survey participants answered correctly regarding the COVID-19 transmission mode and the right measures to avoid acquiring COVID-19 infection. This might be one reason why we did not see the difference in knowledge according to educational background or adequacy of information. Several studies conducted in other Asian countries also showed high level of COVID-19 information in general population.[18] No respondents who used podcast gave wrong answers on COVID-19 transmission and preventive measures. This might be related to low proportion of respondents using this media.

Perception of disease has relevant role in individual's psychological adjustment.[19] WHO has also warned that the risks posed by COVID-19 may generate greater distress, anxiety, anger, and stress.[20] Huang et al study[21] found that 1/3 participants showed anxiety disorders. The possible reason for these mental problems might be related to the "hypochondriac concerns" (worry about being infected) and fear that the epidemic was hard to control.

Assessment regarding anxiety among our study participants showed that most of participants felt worried about their health during COVID-19 pandemic but it did not affect their daily routine life. The source of anxiety among

our study participants was the perceived higher susceptibility in contracting COVID-19, followed by the possibility of more severe COVID-19 course if they got infected and difficulties in their autoimmune drug access during pandemic. Adequate COVID-19 information was related to lower risk of feeling worried which affected daily activities and perception of difficulties in getting medications. Therefore, physicians and other health care providers should advise, give proper information, and comfort their patients, in order to manage their concern and anxiety during pandemic, as higher anxiety may give negative impact in their quality of life.[22,23]

Treatment with hydroxycholoroquine/ chloroquine sulphate was related to higher risk of perception that pandemic would cause difficulties in getting medications, and university education or visiting private clinic were related to lower risk of having that perception. Since the spread of news that hydroxychloroquine can be used to treat COVID-19, there was an increase in hydroxychloroquine demand which lead to its shortage. This condition could make the access of hydroxychloroquine more difficult for autoimmune patients. Before COVID-19 pandemic, the access of hydroxychloroquine had already been difficult due to its availability and price.[24] Most of our respondents used national insurance program. It is important for the government to ensure the availability of medications that are essential for patients with chronic diseases.

Interestingly, treatment with hydroxychloroquine that was also being studied for COVID-19 treatment was related to higher perception of autoimmune medications being able to reduce risk of getting COVID-19 infection. This should be clearly clarified to our patients, so that it will not give sense of false security that loosens proven preventive measures. There is no benefit of hydroxychloroquine treatment for hospitalized patients with COVID-19 in term of 28 days mortality and hospital stay duration.[25] Patients with lupus with or without hydroxychloroquine as baseline therapy have similar risk regarding probability or severity of COVID-19 infection.[26]

Our studies possessed some limitations related to the method of this study. There is also a possibility of bias as some autoimmune patients may not have access to internet to participate in our online survey. The possibility of only autoimmune patients with milder condition that could participate in our online survey should also be considered. Self-reported online survey was affected by patient's honesty and recall memory.

CONCLUSION

Almost all respondents had good knowledge regarding transmission of COVID-19 and did proper practices to prevent COVID-19. Respondents preferred television, medical staff, Whatsapp/Line/Telegram, and Instagram as sources of information. Most of the respondents felt anxious but that did not affect their daily life. Adequacy of information, autoimmune treatment, work from home, educational background, area of living, and health care facilities contributed to perception regarding COVID-19 pandemic.

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REFERENCES

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. who.int. 2020 [cited 30 June 2020]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Novel Coronavirus [Internet]. Who.int. 2020 [cited 30 June 2020]. Available from: https://www.who.int/indonesia/news/novel-coronavirus
3. Maggi E, Canonica GW, Moretta L. COVID-19: Unanswered questions on immune response and pathogenesis. J Allergy Clin Immunol. 2020;146(1):18–22. doi: 10.1016/j.jaci.2020.05.001.
4. Bellone M. Autoimmune Disease: Pathogenesis. eLS. 2015:1-9. doi: 10.1002/9780470015902.a0001276.pub4.

5. Hahn BH, King JK. Treatment of autoimmune disease: established therapies. In: Rose N, Mackay I, eds. The autoimmune diseases. 5th ed. San Diego, London, Waltham: Elsevier; 2014. p. 1209-17.
6. Bedford J, Enria D, Giesecke J, et al. COVID-19: towards controlling of a pandemic. Lancet. 2020;395:1015–8. doi: 10.1016/ S0140-6736(20)30673-5.
7. Desai MK, Brinton RD. Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan. Front Endocrinol (Lausanne). 2019;10:265. doi: 10.3389/fendo.2019.00265.
8. Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? Autoimmune Dis. 2012;2012:ID 251730. doi:10.1155/2012/251730.
9. Pratama MK, Atik N, Hamijoyo L. The pattern of joints involvement in patients with rheumatoid arthritis in Rheumatology Clinic Dr. Hasan Sadikin General Hospital Bandung. Indones J Rheumatol. 2017;9(2):4-7.
10. Wiseman V, Thabrany H, Asante A, et al. An evaluation of health systems equity in Indonesia: study protocol. Int J Equity Health. 2018;17:138. doi: 10.1186/s12939-018-0822-0.
11. Manhendrata Y, Trisnantoro L, Listyadewi S, et al. The Republic of Indonesia Health System Review, Health Systems in Transition. 2017;7(1):1-291. WHO Regional Office for South-East Asia. Available from: https://apps.who.int/iris/handle/10665/254716.
12. Chandrashekara S. The treatment strategies of autoimmune disease may need a different approach from conventional protocol: a review. Indian J Pharmacol. 2012;44(6):665-71. doi: 10.4103/0253-7613.103235.
13. Abd-Alrazaq A, Alhuwail D, Househ M, et al. Top Concerns of Tweeters During the COVID-19 Pandemic: Infoveillance Study. J Med Internet Res. 2020;22(4):e19016. doi: 10.2196/19016.
14. Ko NY, Lu WH, Chen YL, et al. COVID-19-related information sources and psychological well-being: An online survey study in Taiwan. Brain Behav Immun.2020;87:153-4. doi: 10.1016/j.bbi.2020.05.019.
15. Basch CE, Basch CH, Hillyer GC, et al. The Role of YouTube and the Entertainment Industry in Saving Lives by Educating and Mobilizing the Public to Adopt Behaviors for Community Mitigation of COVID-19: Successive Sampling Design Study. JMIR Public Health Surveill. 2020;6(2):e19145. doi:10.2196/19145.
16. Muller J. Number of internet users in Indonesia [Internet]. 2019 [Accessed 2020 June]. 12]. Available from: https://www.statista.com/statistics/254456/number-of-internet-users-in-indonesia/.
17. Saqlain M, Munir MM, Rehman SU, et al. Knowledge, attitude, practice and perceived barriers among healthcare workers regarding COVID-19: a cross-sectional survey from Pakistan. J Hospital Infect. 2020;105:419-23. doi: 10.1016/j.jhin.2020.05.007.
18. Azlan AA, Hamzah MR, Sern TJ, et al. Public knowledge, attitudes and practices towards COVID-19: A cross-sectional study in Malaysia. PLoS ONE. 2020;15(5):e0233668. doi: 10.1371/journal.pone.0233668.
19. Perez-Fuentes MC, Jurado MMM, Ruiz NFO, et al. Questionnaire on Perception of Threat from COVID-19. J Clin Med. 2020;9:1196. doi:10.3390/jcm9041196.
20. World Health Organization. Guidance on routine immunization services during COVID-19 pandemic in the WHO European Region. 2020.
21. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res. 2020;288:112954. doi: 10.1016/j.psychres.2020.112954.
22. Oh C-M, Kim HY, Na HK, et al. The Effect of Anxiety and Depression on Sleep Quality of Individuals With High Risk for Insomnia: A Population-Based Study. Front Neurol. 2019;10:849. doi: 10.3389/fneur.2019.00849.
23. Morgan C, McBeth J, Cordingley L, et al. The influence of behavioural and psychological factors on medication adherence over time in rheumatoid arthritis patients: a study in the biologics era. Rheumatology. 2015;54(10):1780-91. doi: 10.1093/rheumatology/kev105.
24. Yazdany J, Kim AHJ. Use of hydroxychloroquine and chloroquine during the COVID-19 pandemic: what every clinician should know. Ann Int Med. 2020;172(11):754-5. doi: 10.7326/M20-1334.
25. Recovery Trial. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19. Available from: https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19
26. Konig MF, Kim AH, Scheetz MH, et al. Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. Ann Rheum Dis. 2020;79(10):1386–8. doi:10.1136/annrheumdis-2020-217690.

Risk Factors and Laboratory Test Results Associated with Severe Illness and Mortality in COVID-19 Patients: A systematic review

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ABSTRAK

Latar belakang: *tinjauan sistematik ini dilakukan untuk mereviu studi-studi relevan tentang faktor risiko dan hasil pemeriksaan laboratorium yang berhubungan dengan penyakit berat dan kematian pada pasien COVID-19.* ***Metode:*** *kami menggunakan studi systematic review / meta-analisis, studi kohort dan kasus-kontrol yang mencakup kasus supek dan/atau terkonfirmasi COVID-19 yang ditemukan dari penelusuran sistematis di PubMed, Scopus, ProQuest, Wiley Online Library, ScienceDirect dan MedRxiv, serta beberapa studi tambahan yang dicari secara manual. Kami memasukan faktor risiko serta hasil pemeriksaan laboratorium. Risiko bias dinilai menggunakan tool ROBIS-I dan Newcastle-Ottawa Scale. Tipe studi, risiko bias, dan presisi hasil menentukan sufisiensi bukti.* ***Hasil:*** *dari 26 studi, bukti sufisien menunjukkan hubungan antara usia >60 tahun, hipertensi, penyakit jantung koroner, diabetes melitus, level LDH serum 250-500 U/L, LDH > 500 U/L, dan limfopenia (jumlah limfosit darah absolut ≤1.0 109/L) dan penyakit COVID-19 berat. Jumlah sel CD3+CD8+ darah absolut ≤ 75 sel/µl, D-dimer >1 mg/L, AKI stadium 2 dan 3, proteinuria ≥1, hematuria ≥1+, dan level kreatinin serum puncak > 13,26 µmol/L berhubungan dengan kematian.* ***Kesimpulan:*** *usia >60 tahun, hipertensi dan penyakit jantung koroner adalah faktor risiko penyakit COVID-19 berat. Hasil pemeriksaan laboratorium yang berhubungan dengan penyakit berat adalah level LDH serum 250-500 U/L, LDH > 500 U/L dan limfopenia, sedangkan yang berhubungan dengan kematian adalah jumlah sel CD3+CD8+ darah absolut ≤ 75 sel/µl, D-dimer > 1 mg/L, AKI stadium 2 dan 3, proteinuria ≥1, hematuria ≥1+, dan level kreatinin serum puncak > 13,26 µmol/L.*

Kata kunci: *COVID-19, penyakit berat, kematian, faktor risiko, pemeriksaan laboratorium*

ABSTRACT

Background: *we aimed to systematically review all relevant studies related to the risk factors and laboratory test results associated with severe illness and mortality in COVID-19 patients.* ***Methods:*** *we utilised PubMed, Scopus, ProQuest, Wiley Online Library, ScienceDirect and MedRxiv to search for studies, with additional hand-searched journals. We included systematic reviews/meta-analyses, cohort and case control studies of suspected and/or confirmed COVID-19 cases with severe illness and/or mortality as outcomes. We included laboratory test*

results and risk factors. We assessed risk of bias using ROBIS-I and Newcastle-Ottawa Scale assessment tool. Type of study, risk of bias, and precision of results determined evidence sufficiency. ***Results:*** *of 26 records included, sufficient evidence suggested the association between age >60 years, hypertension, coronary heart disease, DM, serum LDH 250-500 U/L, LDH >500 U/L, and lymphopenia (lymphocyte count ≤1.0 x 109 /L) and severe illness of COVID-19. CD3+CD8+ cell count ≤ 75 cell/µl, D-dimer > 1 mg/L, AKI stage 2 and 3, proteinuria ≥1+, hematuria ≥1+, and peak serum creatinine > 13.26 µmol/L are associated with mortality.* ***Conclusion:*** *age >60 years, hypertension, DM, and coronary heart disease are the risk factors for severe illness of COVID-19. Laboratory test results associated with severe illness are serum LDH 250-500 U/L, LDH >500 U/L, and lymphopenia, whereas test results associated with mortality are CD3+CD8+ cell count ≤ 75 cell/µl, AKI stage 2 and 3, proteinuria ≥1+, hematuria ≥1+, D-dimer > 1 mg/L, peak serum creatinine > 13.26 µmol/L.*

Keywords: *COVID-19, severe illness, mortality, risk factor, laboratory test.*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is a problem in more than 210 countries. As of 12 Aug 2020, the global case fatality rate as high as 3.6%.[1] The case fatality rate was much higher in early pandemic era in various developing and developed countries. In severe cases, patients with SARS-CoV-2 infection may require respiratory support or cardio-respiratory support in the form of mechanical ventilation or extra-corporeal membrane oxygenation (ECMO), respectively. Moreover, previous studies reported that respiratory failure was found in nearly half of the fatalities of COVID-19 patients.[2,3]

The great interest in COVID-19 has led researchers to conduct studies about the risk factors for adverse outcomes in COVID-19. Although numerous studies of varying study design and quality reported potential risk factors and laboratory test results associated with severe illness and mortality, the results remain inconclusive.[4-7] Several studies were not able to provide causal mechanisms to link risk factors and outcomes.[4,6] Furthermore, several systematic reviews/ meta-analyses (SR/MA) in this field provided substandard quality of analyses. High case fatality rate, inconclusive study results, and substandard quality of analysis led us us to conduct a systematic review in this field and to assess the quality of evidence in a careful manner subsequently.

In this systematic review, we examined primary observational studies as well as existing SR/MA. Due to the ever-growing body of evidence, we also took into account common laboratory results that indicated clinical conditions associated with unfavourable outcomes of COVID-19. We adopted systematic approach to confirm and summarise the evidence regarding risk factors and laboratory test results associated with severe illness and mortality in COVID-19 patients. Finally, we elucidated the proposed mechanisms of the risk factors affecting the course of the disease and their influence on disease outcomes.

METHODS

Search strategy and selection criteria

We registered our review protocol on PROSPERO with registration number CRD42020185424.[8] A literature search was conducted systematically using electronic databases, namely PubMed, Scopus, ProQuest, Wiley Online Library, ScienceDirect, and MedRxiv. Articles hand-searched from the authors' personal files were also included. Only full-text articles published in English between 1 January and 13 April 2020 were taken into account. The search strategies are shown in **Table 1**.

Selection of Studies

We selected studies based on predefined eligibility criteria. We included all systematic reviews, meta-analyses, and primary observational studies (cohort and case–control studies) of patients of any age with suspected and/or confirmed COVID-19. The selected risk factors included, but were not limited to: (1)

Table 1. Keywords for search strategies

Database	Search query	Hits
Pubmed	Search ((((((((((SARS-CoV-2[Title/Abstract)) OR SARS-CoV-2[MeSH Terms]) OR 2019-nCOV[Title/Abstract]) OR 2019-nCOV[MeSH Terms]) OR COVID-19[Title/Abstract]) OR COVID-19[MeSH Terms]) OR Wuhan coronavirus[Title/Abstract]) OR Wuhan coronavirus[MeSH Terms])))) AND ((((((((((((((((((((mortality[Title/Abstract]) OR mortality[MeSH Terms]) OR death[Title/Abstract]) OR death[MeSH Terms]) OR ventilators[Title/Abstract]) OR ventilators[MeSH Terms]) OR ARDS[Title/Abstract]) OR acute respiratory distress syndrome[Title/Abstract]) OR ARDS[MeSH Terms]) OR acute respiratory distress syndrome[MeSH Terms]) OR ECMO[Title/Abstract]) OR ECMO[MeSH Terms]) OR Extracorporeal Membrane Oxygenation[Title/Abstract]) OR Extracorporeal Membrane Oxygenation[MeSH Terms]) OR severe illness[Title/Abstract]) OR severe illness[MeSH Terms]))))))	373
Scopus	TITLE-ABS-KEY ((sars-cov-2 OR 2019-ncov OR wuhancoronavirus OR covid-19) AND (mortality OR death OR ventilators OR ards OR acuterespiratorydistresssyndrome OR ecmo OR extracorporealmembraneoxygenation OR severeillness))	208
ProQuest	ab(SARS-CoV-2 OR 2019-nCOV OR Wuhancoronavirus OR COVID-19) AND ab(mortality OR death OR ventilators OR ARDS OR acute respiratory distress syndrome OR ECMO OR Extracorporeal Membrane Oxygenation OR severe illness)	153
MedRxiv	"(SARS-CoV-2 OR 2019-nCOV OR Wuhancoronavirus OR COVID-19) AND (mortality OR death OR severe illness OR ARDS OR ECMO)"	810
Wiley Online Library	((sars-cov-2 OR 2019-ncov OR wuhancoronavirus OR covid-19) AND (mortality OR death OR ventilators OR ards OR acuterespiratorydistresssyndrome OR ecmo OR extracorporealmembraneoxygenation OR severeillness))	91
ScienceDirect	((SARS-CoV-2 OR 2019-nCOV OR Wuhancoronavirus OR COVID-19) AND (mortality OR death OR ventilators OR ARDS OR acute respiratory distress syndrome OR ECMO OR Extracorporeal Membrane Oxygenation OR severe illness))Filter:2020	158

clinical characteristics (e.g., age, sex, history of smoking, body mass index [BMI]); (2) clinical symptoms (e.g., dyspnoea, fever, cough); (3) duration of symptoms; (4) time from first medical visit to admission; (5) comorbidities (e.g., cardio-vascular disease and chronic obstructive pulmonary disease [COPD]), current or history of treatment (e.g., history of chest operation, ongoing chemotherapy); (6) healthcare resource constraint; (7) blood type; (8) coinfections (e.g., other viral or bacterial infections); and (9) low presenting oxygen saturation. We also considered laboratory test results such as serum lactate, platelet count, neutrophil-to-lymphocyte-ratio (NLR), acute cardiac injury markers, C-reactive protein (CRP), coagulation markers, and serum cytokines.

The main outcomes were severe illness and mortality of COVID-19. We defined COVID-19 severe illness as SARS-CoV-2 infection resulting in severe COVID-19 disease, acute respiratory distress syndrome (ARDS) based on the Berlin definition,[9] intensive care unit (ICU) admission, mechanical ventilation requirement, and/or ECMO requirement. Severe COVID-19 disease in the teenage, adult, and older adult population was defined as a suspected or confirmed case of COVID-19 with at least one of the following symptoms: respiratory rate ≥30 bpm; pulse oximeter <93% saturation in room air; and PaO_2/FiO_2 ratio ≤300 mm Hg. Severe COVID-19 disease in children was defined as cough or shortness of breath, with at least one of the following symptoms: central cyanosis or pulse oximeter <90% saturation in room air, severe respiratory distress, abnormal chest retractions; sign(s) of severe pneumonia, such as poor feeding, inability to tolerate oral intake, lethargy, change in mental status, and seizure.

First, we excluded duplications from the articles collected from the initial electronic databases. Second, we selected articles based on the predetermined eligibility criteria. Selection was done through initial title and abstract screening, followed by full-text screening. The selection process involved a minimum of two independent reviewers. Conflicting decisions were resolved by discussion between two

reviewers, or consultation with a third reviewer, if required.

Quality Assessment and Data Extraction

Risk of bias of each study was assessed for each outcome, namely severe illness and death. Risk of bias assessment was performed on all articles chosen through a careful selection process. Two independent reviewers conducted the assessment using certain assessment tools. Systematic review was assessed using ROBIS-I,[10] whereas the assessment of the observational studies relied on the Newcastle-Ottawa Scale (NOS) assessment tool.[11] There are four domains in ROBIS-I (i.e., study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings) consisting of 21 items in total. Risk of bias was determined by the final three domains in ROBIS-I. The interpretation of ROBIS-I was categorised as high, low, or unclear risk of bias.

The NOS assessment has three domains consisting of selection, comparability, and exposure. There are four items, one item, and two items in the selection, comparability, and exposure domain, respectively. In the selection and exposure domains, there are several possible answers to each question and the highest answer is marked with a "star", presented as number in this systematic review. In the comparability domain, there are two possible stars given if there is adjustment of other controlled factors. In this review, we classified the results of NOS assessment as low risk and high risk of bias. Only studies with full stars in all domains were considered as having a low risk of bias.

The data extraction process involved at least two independent reviewers. Disagreement required discussion and subsequent involvement of the third reviewer as needed. In the case of incomplete data of the study, the systematic review team contacted the author. The measures of effect of interest were limited to relative risk (RR), odds ratio (OR), or hazard ratio (HR).

Data Synthesis

We planned to pool primary studies providing usable data in any single meta-analysis as clinically homogeneous with Review Manager 5 using a fixed-effect model. If a single true effect was not obtained due to the variety of population and exposures or substantial heterogeneity, we planned to use a random-effect or narrative review method. Subgroup analysis was planned to be performed on the data of special populations of COVID-19 patients, e.g., patients with underlying malignancy. Sufficiency of evidence was determined by the type of

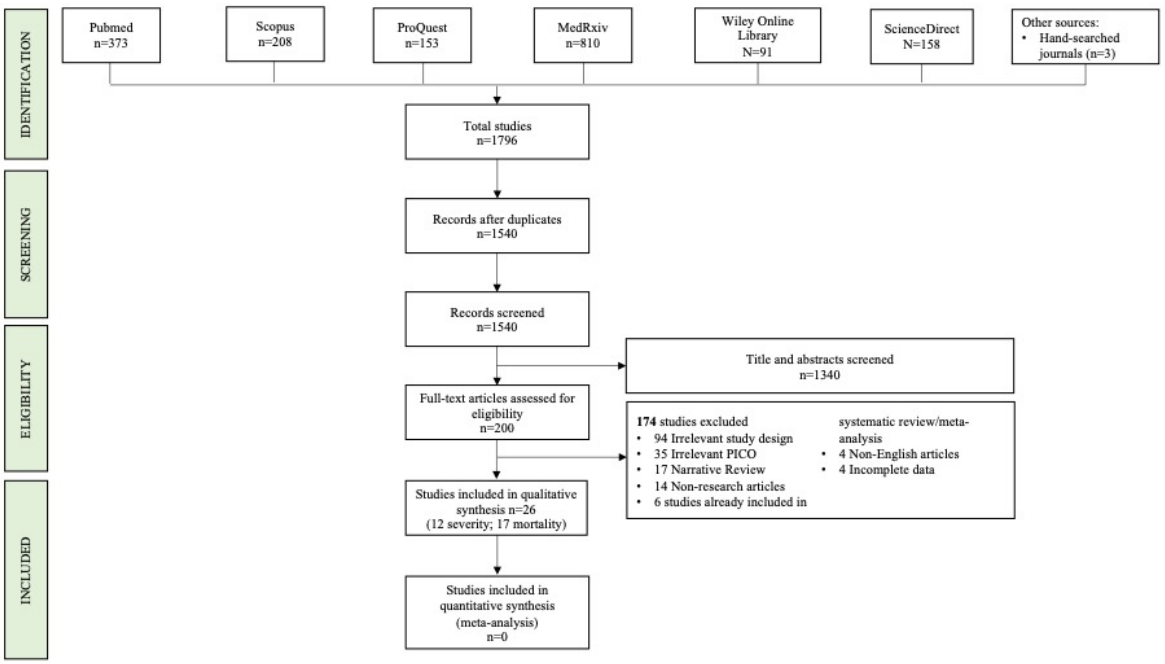

Figure 1. PRISMA diagram of this systematic review.

study, risk of bias, and precision of results. We considered the evidence was sufficient if supported by the best study design with low risk of bias and precise results.

RESULTS

We retrieved 1,796 records, consisting of 1,793 records from four electronic databases and three from other hand-searched journals (**Figure 1**).

We used a PRISMA flow diagram to illustrate our literature searching strategy.[12] After removing duplicates, each of 1,540 title and abstract records was assessed by at least two of nine reviewers (SS, SRFS, KH, EDS, RR, YP, WW, MKA, JM) independently. There were 200 records identified by the full text for further assessment of eligibility. We excluded 170 studies that did not meet our eligibility criteria as well as excluding primary studies identified in SR/MA. In addition, four other studies with incomplete outcome data were excluded. We have contacted the authors but received no response. Finally, there were 26 records included in this study.

Most of the studies were conducted in China, followed by France, Germany, Singapore, and the USA. There were ten journal pre-proofs (e.g. in medRxiv) as noted in **Table 2**. We did not find any articles that included a paediatric population.

Table 2. List of included studies and databases

Author (Publication Year)	Title	Journal
Zuin (2020)	Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis	Journal of Infection
Tang (2020)	Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy	J Thromb Haemost
Zhou (2020)	A New Predictor of Disease Severity in Patients with COVID-19 in Wuhan, China	Pre-proof (Medrxiv)
Zhou (2020)	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	The Lancet
Fu (2020)	Influence factors of death risk among COVID-19 patients in Wuhan, China: a hospital-based case-cohort study	Pre-proof (Medrxiv)
Shi (2020)	Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China	JAMA
Lippi (2020)	Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis	Polish Arch Intern Med
Cheng (2020)	Kidney disease is associated with in-hospital death of patients with COVID-19	Kidney International
Simonnet (2020)	High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation	Obesity (Silver Spring)
Ma (2020)	COVID-19 Myocarditis and Severity Factors: An Adult Cohort Study	Pre-proof (Medrxiv)
Zhang (2020)	Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: A single center retrospective cohort study	Pre-proof (Medrxiv)
Barrasa (2020)	SARS-Cov-2 in Spanish Intensive Care: Early Experience with 15-day Survival In Vitoria	Anaesth Crit Care Pain Med
Lippi (2020)	Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis	Clin Chim Acta
Chen (2020)	Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis	Pre-proof (Medrxiv)
Matsushita (2020)	The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis	Pre-proof (Medrxiv)
Roncon (2020)	Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome	Journal of Clinical Virology
Xie (2020)	Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19	Pre-proof (Medrxiv)

Table 2. List of included studies and databases

Author (Publication Year)	Title	Journal
Jain (2020)	Systematic review and meta-analysis of predictive symptoms and comorbidities for severe COVID-19 infection	Pre-proof (Medrxiv)
Parohan (2020)	Risk factors for mortality of adult inpatients with Coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of retrospective studies	Pre-proof (Medrxiv)
Alqahtani (2020)	Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis	Plos One
Du (2020)	Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study	European Respiratory Journal
Ji (2020)	Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score	Clinical Infectious Diseases
Wang (2020)	Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up.	Journal of Infection
Zhang (2020)	Comorbid Diabetes Mellitus was Associated with Poorer Prognosis in Patients with COVID-19: A Retrospective Cohort Study	Pre-proof (Medrxiv)
Liu (2020)	Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19	Journal of Infection
Lippi (2020)	Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis	Clin Chim Acta

Table 3. Characteristics of included study of severe illness and mortality.

First author	Publication year	Country	Study design	Number of participants	Follow-up Period	Risk Factors
Severe Illness						
Alqahtani[14]	2020	China and USA	SR/MA	2473	N/A	COPD, Smokers
Chen[15]	2020	China	SR/MA	1936	N/A	Hypertension, Diabetes mellitus, Coronary heart disease
Lippi (a)[16]	2020	China	SR/MA	2552	N/A	Hypertension
Lippi (b)[17]	2020	China and Singapore	SR/MA	1289	N/A	Thrombocytopenia
Lippi (c)[13]	2020	China	SR/MA	N/R	N/A	PCT
Matsushita[4]	2020	China	SR/MA	51845	N/A	Male, Smokers, Hypertension, Diabetes mellitus
Roncon[18]	2020	China	SR/MA	1382	N/A	Diabetes Mellitus
Jain[5]	2020	China	SR/MA	1813	N/A	Male, Dyspnoea, Cough, Fever, Fatigue, Myalgia, Expectoration, Headache, COPD, Diabetes mellitus, CVD, Hypertension
Ma[19]	2020	China	Case-control	84	41 days	Age, Diabetes mellitus, Ct value of SARS-CoV-2, PIIa
Zhou (b)[29]	2020	China	Case-control	377	N/R	Agea, NLRa, CRP, D-dimera
Simonnet[21]	2020	France	Prospective Cohort	124	2-40 days	BMI (obese vs non obese), BMI (severe obese vs non severe obese), Age, Male, Diabetes mellitus, Hypertension, Dyslipidaemia
Ji[22]	2020	China	Retrospective Cohort	208	18-58 days	Age (>60 years old), Lymphocyte (≤1.0x10^9/L), D-dimer (>0.55 mg/L), LDH (250-500 U/L), LDH (>500 U/L)

Table 3. Characteristics of included study of severe illness and mortality.

First author	Publication year	Country	Study design	Number of participants	Follow-up Period	Risk Factors
Mortality						
Alqahtani[14]	2020	China and USA	SR/MA	2473	N/A	COPD
Parohan[23]	2020	China	SR/MA	22350	N/A	Age (≥ 65 years old), Male, Hypertension, Diabetes mellitus, COPD, CVD
Lippi (a)[16]	2020	China	SR/MA	2552	N/A	Hypertension
Roncon[18]	2020	China	SR/MA	1382	N/A	Diabetes mellitus
Zuin[24]	2020	China	SR/MA	302	N/A	Arterial hypertension
Tang[25]	2020	China	Case-control	449	29-72 days	Agea, Sex ratioa, PTa, D-dimer[a], Platelet Count[a], treating with heparin
Wang[6]	2020	China	Case-control	339	28 days	COPD, Cardiovascular disease, Cerebrovascular disease, Acute cardiac injury, Arrhythmia, AKI, ARDS, Cardiac insufficiency, Bacterial infection
Barrasa[26]	2020	Spain	Prospective Cohort	48	15 days	PCT >0.5 vs ≤0.5 µmol/L and PCT >1.0 vs ≤1.0 µmol/L
Cheng[27]	2020	China	Prospective Cohort	701	18-32 days	Proteinuria, Haematuria, Elevated BUN[a], Elevated Serum Cr[a], AKI Stage 1-3
Fu[28]	2020	China	Prospective Cohort	200	N/R	Age (> 70 years old), Male, Smokers, Hypertension, Diabetes mellitus, Cardiac disease, Chronic pulmonary disease, Oxygenation index on admission, Myoglobin, Alanine aminotransferase[a], Total bilirubin[a], Creatininea, Urea nitrogena, Uric acid[a], Creatine kinase[a], LDH[a], Aspartate aminotransferase[a], Aspartate/alanine ratio[a]
Shi[7]	2020	China	Prospective Cohort	416	5-26 days	Age[a], CAD, CVD, Diabetes mellitus, COPD, Chronic renal failure, Cancer, ARDS, Cardiac injury, Creatinine ≥ 13.26 µmol/L, nt-pro-BNP ≥ 106,42 pmol/L
Du[29]	2020	China	Retrospective Cohort	179	Minimum 46 days	Age (≥ 65 years old), CVD, CD3CD8+≤ 75 cell/µL, TnI ≥ 0.05 ng/mL
Liu[30]	2020	China	Retrospective Cohort	245	1-59 days	NLR Tertile 2 (2.21-4.82), NLR Tertile 3 (4.85-88.09)
Zhang (a)[31]	2020	China	Retrospective Cohort	258	29-43 days	Diabetes mellitus
Zhang (b)[32]	2020	China	Retrospective Cohort	48	N/R	Age[a], SpO2%[a], Serum Cr[a], D-dimer per 1 mg/L increase, hs-TnI ≥ 0.026 mcg/L
Zhou (a)[33]	2020	China	Retrospective Cohort	191	33 days	Age per 1 year increase, CAD, SOFA[a], Lymphocyte (per 1x109/L increase), D-dimer (> 0.5 or >1) vs ≤0.5 mg/L
Xie[34]	2020	China	Retrospective Cohort	299	60 days	Age[a], LDH[a], Log Lymphocyte count[a], SpO2%[a]

SR/MA: Systematic Review/Meta-analysis, PCT: procalcitonin, CVD: cardiovascular disease, LDH: lactate dehydrogenase, N/R: not reported, N/A: not applicable, PT: prothrombin time, AKI: acute kidney injury, ARDS: acute respiratory distress syndrome, BUN: blood urea nitrogen, Cr: creatinine, TnI: troponin I, hs-cTnI: high sensitivity troponin I, CAD: coronary artery disease, SOFA: Sequential Organ Failure Assessment.
[a] The article did not mention the cut-off point.

There were 12 and 17 included studies describing the factors related to severe illness and mortality of COVID-19 infection, respectively (**Table 3**). Among the studies reporting severe illness, there were eight SR/MA, two case–control, and two cohort studies. Most studies were conducted in China. The number of subjects included was between 84 and 51,845, with one study not mentioning the number of participants.[13]

There were five SR/MA, two case–control, four prospective cohort, and six retrospective cohort studies reporting risk factors related to the mortality of COVID-19 patients. The number of subjects ranged from 48 to 22,350.

There were four out of 12 cohort studies with low risk of bias[22,27,29,33] (**Table 4**). All of the case–control studies had high risk of bias (**Table 5**). Only one in ten SR/MA had low risk of bias (**Table 6**),[15] whereas the remainder had high risk of bias due to lack of information regarding study eligibility and identification and selection of patients.

Risk Factors for Severe Illness and Mortality of COVID-19

We identified several risk factors related to severe illness and mortality of COVID-19

Table 4. The assessment of risk of bias of the cohort study using Newcastle Ottawa scale[a]

Study	Selection				Comparability (C)	Outcome			Risk of Bias
	REC	SNEC	AE	DO		AO	FU	AFU	
Severe Illness									
Ji, 2020[22]	1	1	1	1	2	1	1	1	Low
Simonnet, 2020[21]	0	1	1	1	1	0	0	1	High
Mortality									
Du, 2020[29]	1	1	1	1	2	1	1	1	Low
Zhang, 2020b[32]	1	1	1	1	2	1	0	1	High
Liu, 2020[30]	1	1	1	1	2	1	0	1	High
Barrasa, 2020[26]	0	1	1	1	0	1	1	1	High
Xie, 2020[34]	1	1	1	1	1	1	1	0	High
Zhang, 2020a[31]	0	1	1	1	1	1	1	1	High
Fu, 2020[28]	1	1	1	1	1	1	0	1	High
Cheng, 2020[27]	1	1	1	1	2	1	1	1	Low
Shi, 2020[7]	0	1	1	1	1	1	0	1	High
Zhou, 2020[33]	1	1	1	1	2	1	1	1	Low

[a]1 representing 1 star
REC: Representativeness of the exposed cohort, SNEC: Selection of the non-exposed cohort, AE: Ascertainment of exposure, DO: Demonstration that outcome of interest was not present at start of study, C: Comparability of cohorts on the basis of the design or analysis, AO: Assessment of outcome, FU: Was follow-up long enough for outcomes to occur, AFU: Adequacy of follow up of cohorts.

Table 5. The assessment of risk of bias of the case-control study using Newcastle Ottawa scale[a]

Study	Selection				Comparability (C)	Outcome			Risk of Bias
	ACD	RC	SC	DC		AE	SMA	NRR	
Severe Illness									
Ma, 2020[19]	1	1	0	1	1	1	1	0	High
Zhou, 2020b[20]	1	0	0	1	0	1	1	0	High
Mortality									
Tang, 2020[25]	1	1	0	1	0	1	1	0	High
Wang, 2020[6]	1	1	0	1	2	1	1	0	High

[a]1 representing 1 star
ACD: Adequate case definition, RC: Representativeness of the cases, SC: Selection of Controls, DC: Definition of Controls, C: Comparability of cases and controls on the basis of the design or analysis, AE: Ascertainment of exposure, SMA: Same method of ascertainment for cases and controls, NRR: Non-response rate.

Table 6. The assessment of risk of bias of the systematic review/meta-analysis using ROBIS-I

Outcome	Phase 2				Phase 3
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Severe Illness					
Alqahtani, 2020[14]	H	H	L	L	H
Chen, 2020[15]	L	H	L	L	L
Jain 2020[5]	L	H	H	H	H
Lippi, 2020a[16]	L	L	H	H	H
Lippi, 2020b[17]	L	H	H	H	H
Lippi, 2020c[13]	H	H	H	H	H
Matsushita, 2020[4]	H	H	L	L	H
Roncon, 2020[18]	H	H	L	L	H
Mortality					
Alqahtani, 2020[14]	H	H	L	L	H
Lippi, 2020a[16]	L	L	H	L	H
Parohan, 2020[23]	L	H	L	L	H
Roncon, 2020[18]	H	H	L	L	H
Zuin, 2020[24]	H	H	L	L	H

H: High risk of bias; L: Low risk of bias

that consisted of signs and symptoms, clinical characteristics, and comorbidities (**Table 7**).

The included studies that related to clinical characteristics reported four risk factors, namely older age, male sex, high BMI, and history of smoking. Age >60 years was associated with severe illness with OR 3.00 (95% confidence interval [CI) 1.40–6.00).[22] One study with high risk of bias reported older age linked to mortality with HR,OR 2.39 (1.75–3.28).[2]

Other reported risk factors were male sex and high BMI. Two of three studies reported an association between male sex and severe illness,[4,21] but there was no significant association reported by two included studies for mortality.[23,28] One observational study reported that a high BMI ($\geq$35 kg/m^2) is associated with severe illness.[21] We found varying results pertaining to smoking history.[4,14,28]

Reported comorbidities related to severe illness and mortality of COVID-19 were hypertension, diabetes mellitus (DM), cardio-vascular disease, and COPD. Coronary heart disease was also reported to have an association with severe illness with OR 2.85 (95% CI 1.68–4.84).[15] In addition, other comorbidities related to mortality were cerebrovascular disease, chronic renal failure, and cancer. Four out of five studies reported that hypertension was associated with severe illness,[4,5,15,16] whereas three out of four studies reported an association with mortality.[16,18,23] Four out of five studies reported that DM was associated with severe illness,[4,5,15,18] and three out of five studies reported an association with mortality.[18,23,31] Most of the studies had high risk of bias except one study by Chen and colleagues.[15] Several studies supporting the role of other comorbidities, such as COPD, cardio-vascular disease, and cerebrovascular disease, had high risk of bias and variable conclusions.[6,7,14,23,28,29,33]

Systematic review/meta-analyses with high risk of bias, reported several signs and symptoms as risk factors for severe infection, such as dyspnoea, cough, fever, expectoration, headache, fatigue, and myalgia.[5] Among the suggested risk factors, dyspnoea and cough had OR of 3.70 (95% CI 1.83–7.46) and 1.63 (95% CI 1.03–2.60), respectively.[5]

We identified several studies related to cardio-vascular disease as a risk factor for mortality. However, we did not conduct a meta-analysis for this variable due to the potential heterogeneity among the studies, such as study design and follow-up period.

Table 7. Risk factors for severe illness and mortality

Type of Variable	Type of Study	Author	Total (N)	Severe Illness (N)	Type of Estimate Effect	Effect Estimate (95% CI)	Risk of Bias
Severe Illness							
Clinical Characteristics							
Age > 60 years old	Observational	Ji[22]	N/R	N/R	HR	3.0 (1.40 to 6.00)	Low
Age per 10 year increase	Observational	Ma[19]	84	N/R	OR	2.35 (1.21 to 4.58)	High
Male	SR/MA	Matsushita[4]	43396	N/R	OR/HR	1.70 (1.52 to 1.89)	High
	SR/MA	Jain[5]	908	104	OR	1.15 (0.89 to 1.48)	High
	Observational	Simonnet[21]	124	64	OR	2.83 (1.02 to 7.85)	High
BMI > 30 kg/m^2	Observational	Simonnet[21]	89	48	OR	3.45 (0.83 to 14.31)	High
BMI ≥ 35 kg/m^2	Observational	Simonnet[21]	65	30	OR	7.36 (1.63 to 33.14)	High
Current smokers[a]	SR/MA	Alqahtani[14]	916	31	RR	1.45 (1.03 to 2.04)	High
Smokers[a]	SR/MA	Matsushita[4]	1342	N/R	OR/HR	2.01 (0.83 to 4.86)	High
Comorbidities							
Hypertension	SR/MA	Lippi (a)[16]	2552	243	OR	2.49 (1.98 to 3.12)	High
	SR/MA	Matsushita[4]	24351	N/R	OR/HR	2.74 (2.12 to 3.54)	High
	SR/MA	Chen[15]	1936	117	OR	2.3 (1.76 to 3.00)	Low
	SR/MA	Jain[5]	212	16	OR	1.97 (1.40 to 2.77)	High
	Observational	Simonnet[21]	124	48	OR	2.29 (0.89 to 5.84)	High
Diabetes mellitus	SR/MA	Matsushita[4]	24403	N/R	OR/HR	2.81 (2.01 to 3.93)	High
	SR/MA	Chen[15]	1936	67	OR	2.67 (1.91 to 3.74)	Low
	SR/MA	Roncon[18]	1380	41	OR	2.79 (1.85 to 4.22)	High
	SR/MA	Jain[5]	105	7	OR	3.12 (1.00 to 9.75)	High
	Observational	Simonnet[21]	124	23	OR	1.6 (0.44 to 5.83)	High
Cardiovascular disease	SR/MA	Matsushita[4]	22612	N/R	OR/HR	3.58 (2.06 to 6.21)	High
	SR/MA	Jain[5]	53	2	OR	2.7 (1.52 to 4.80)	High
Coronary heart disease	SR/MA	Chen[15]	335	28	OR	2.85 (1.68 to 4.84)	Low
COPD	SR/MA	Jain[5]	19	1	OR	6.42 (2.44 to 16.9)	High
	SR/MA	Alqahtani[14]	35	22	RR	1.88 (1.40 to 2.40)	High
Dyslipidaemia	Observational	Simonnet[21]	124	24	OR	0.68 (0.24 to 1.97)	High
Sign and Symptoms							
Dyspnoea	SR/MA	Jain[5]	262	37	OR	3.70 (1.83 to 7.46)	High
Cough	SR/MA	Jain[5]	1040	157	OR	1.63 (1.03 to 2.60)	High
Fever	SR/MA	Jain[5]	913	129	OR	1.17 (0.88 to 1.56)	High
Expectoration	SR/MA	Jain[5]	392	24	OR	1.75 (0.63 to 4.83)	High
Headache	SR/MA	Jain[5]	181	4	OR	1.16 (0.78 to 1.74)	High
Fatigue	SR/MA	Jain[5]	586	57	OR	1.44 (0.76 to 2.72)	High
Myalgia	SR/MA	Jain[5]	187	7	OR	1.32 (0.89 to 1.96)	High
Mortality							
Clinical Characteristics							
Age (≥ 65 vs <65 years)	SR/MA	Parohan[23]	22350	N/R	HR,OR	2.39 (1.75 to 3.28)	High
Age (≥ 65 vs <65 years)	Observational	Du[29]	179	17	OR	3.765 (1.15 to 17.39)	Low

Table 7. Risk factors for severe illness and mortality

Type of Variable	Type of Study	Author	Total (N)	Severe Illness (N)	Type of Estimate Effect	Effect Estimate (95% CI)	Risk of Bias
Age (50-59 vs <49 years)	Observational	Fu[28]	102	8	RR	3.698 (0.83 to 16.57)	High
Age (60-69 vs <49 years)	Observational	Fu[28]	108	7	RR	2.907 (0.63 to 13.36)	High
Age (>70 vs <49 years)	Observational	Fu[28]	88	17	RR	10.679 (2.62 to 43.46)	High
Age per 1 Unit increase	Observational	Zhou[33]	191	N/R	OR	1.10 (1.03 to 1.17)	Low
Male	SR/MA	Parohan[23]	22086	N/R	HR,OR	1.25 (0.75 to 2.09)	High
	Observational	Fu[28]	200	16	RR	0.907 (0.49 to 1.68)	High
Smokers[a]	Observational	Fu[28]	170	16	RR	0.809 (0.44 to 1.48)	High
Comorbidities							
Hypertension	SR/MA	Zuin[24]	302	47	OR	3.36 (1.96 to 7.74)	High
	SR/MA	Parohan[23]	21640	652	HR,OR	3.29 (1.54 to 7.05)	High
	SR/MA	Lippi (a)[16]	341	55	OR	2.42 (1.51 to 3.90)	High
	Observational	Fu[28]	200	22	RR	1.797 (0.94 to 3.43)	High
Diabetes mellitus	SR/MA	Roncon[18]	354	26	OR	3.21 (1.82 to 5,64)	High
	SR/MA	Parohan[23]	21376	634	HR,OR	3.11 (1.10 to 8.80)	High
	Observational	Zhang (b)[31]	258	7	HR	2.84 (1.01 to 8.01)	High
	Observational	Fu[28]	200	26	RR	1.495 (0.72 to 3.11)	High
	Observational	Shi[7]	416	60	HR	0.75 (0.38 to 1.50)	High
COPD	SR/MA	Alqahtani[14]	167	10	RR	1.1 (0.60 to 1.80)	High
	SR/MA	Parohan[23]	21175	590	OR	7.69 (5.65 to 10.47)	High
	Observational	Wang[6]	339	11	HR	2.24 (1.12 to 4.50)	High
	Observational	Shi[7]	416	12	HR	0.39 (0.04 to 3.68)	High
Cardiovascular disease	Observational	Wang[6]	339	21	HR,OR	1.858 (1.06 to 3.26)	High
	Observational	Fu[28b]	200	2	RR	0.719 (0.19 to 2.73)	High
	Observational	Shi[7]	416	44	HR	1.40 (0.65 to 3.03)	High
	Observational	Zhou[33]	191	13	OR	2.14 (0.26 to 17.79)	Low
Cerebrovascular disease	SR/MA	Parohan[23]	21175	590	OR	7.39 (2.88 to 18.96)	High
	Observational	Wang[6]	339	10	HR,OR	1.379 (0.65 to 2.93)	High
Cardiovascular or cerebrovascular diseases	Observational	Du[29]	179	12	OR	2.464 (0.76 to 8.04)	Low
Chronic pulmonary disease	Observational	Fu[28]	200	4	RR	3.2 (1.486 to 6.89)	High
Chronic renal failure	Observational	Shi[7]	416	17	HR	0.66 (0.29 to 1.46)	High
Cancer	Observational	Shi[7]	416	9	HR	0.82 (0.18 to 3.65)	High

[a] There is uncertainty of the length of exposure
[b] The author described as cardiac disease

Laboratory Test Results Associated with Severe Illness and Mortality of COVID-19

The laboratory test results associated with severe illness and mortality are shown in **Table 8**. The role of thrombocytopenia as a test result associated with severe illness was reported by one SR/MA with OR 5.13 (95% CI 1.81–14.58).[17] There was also a reported association between

Table 8. Laboratory and other test results for severe illness and mortality of COVID-19.

Type of Variable	Type of Study	Author	Total (N)	Severe Illness (N)	Type of Estimate Effect	Effect Estimate (95% CI)	Risk of Bias
Severe Illness							
Thrombocytopeniaa	SR/MA	Lippi (b)[17]	1289	113	OR	5.13 (1.81 to 14.58)	High
LDH 250-500 U/L	Observational	Ji[22]	202	24	HR	2.5 (1.20 to 5.20)	Low
LDH >500 U/L	Observational	Ji[22]	131	5	HR	9.8 (2.80 to 33.80)	Low
PCT ≥ 0.50 µmol/L	SR/MA	Lippi (c)[13]	N/A	N/R	OR	4.76 (2.74 to 8.29)	High
Lymphocyte (≤1.0x10^9/L)	Observational	Ji[22]	208	N/R	HR	3.7 (1.80 to 7.80)	Low
D-dimer >0.55 mg/L	Observational	Ji[22]	208	16	HR	1.0 (0.50 to 2.10)	Low
CT-Value of SARS-CoV-2 ≤36.67 vs moreb	Observational	Ma[19]	84	N/R	OR	0.158 (0.03 to 0.99)	High
Mortality							
Lymphocyte count per 1 Unit increase (x109/L)	Observational	Zhou[33]	191	N/R	OR	0.19 (0.02 to 1.62)	Low
CD3+CD8+ ≤ 75 cell/mcL	Observational	Du[29]	179	17	OR	5 (1.32 to 18.96)	Low
NLR tertile 2 (2.21-4.82)	Observational	Liu[30]	163	5	OR	1.71 (0.14 to 21.38)	High
NLR tertile 3 (4.85-88.09)	Observational	Liu[30]	164	26	OR	16.61 (1.58 to 74.66)	High
Acute cardiac injuryc	Observational	Wang[6]	339	39	HR	1.547 (0.75 to 3.193)	High
	Observational	Shi[7]	416	42	HR	3.41 (1.62 to 7.16)	High
Cardiac Troponin I ≥ 0.05 ng/mL	Observational	Du[29]	179	13	OR	7.2 (1.52 to 34.14)	Low
Myoglobin Positive	Observational	Fu[28]	200	13	OR	0.643 (0.23 to 1.82)	High
hs-cTropI ≥ 0.026 mcg/L	Observational	Zhang (a)[32]	48	10	HR	10.902 (1.28 to 92.93)	High
Arrhythmia	Observational	Wang[6]	339	13	HR	0.754 (0.37 to 1.53)	High
Cardiac Insufficiencyd	Observational	Wang[6]	339	25	HR	1.105 (0.59 to 2.06)	High
nt-proBNP ≥ 106,42 pmol/L	Observational	Shi[7]	416	N/A	HR	1.52 (0.74 to 3.10)	High
AKI	Observational	Wang[6]	339	17	HR	1.159 (0.55 to 2.41)	High
AKI stage 1e	Observational	Cheng[27]	701	13	HR	1.90 (0.76 to 4.75)	Low
AKI stage 2e	Observational	Cheng[27]	701	9	HR	3.53 (1.50 to 8.27)	Low
AKI stage 3e	Observational	Cheng[27]	701	14	HR	4.72 (2.55 to 8.75)	Low
Proteinuria 1+ vs Negative	Observational	Cheng[27]	701	N/R	HR	2.47 (1.15 to 5.33)	Low
Proteinuria 2+/3+ vs Negative	Observational	Cheng[27]	701	N/R	HR	6.80 (2.97 to 15.56)	Low
Hematuria 1+ vs Negative	Observational	Cheng[27]	701	N/R	HR	3.05 (1.43 to 6.49)	Low
Hematuria 2+/3+ vs Negative	Observational	Cheng[27]	701	N/R	HR	8.89 (4.41 to 17.94)	Low
Peak Serum Cr >13.26 µmol/L	Observational	Cheng[27]	701	N/R	HR	3.09 (1.95 to 4.87)	Low
Creatinine ≥13.26 µmol/L	Observational	Shi[7]	416	N/R	HR	1.22 (0.60 to 2.50)	High
ARDS	Observational	Wang[6]	339	56	HR	29.332 (12.36 to 69.58)	High

Table 8. Laboratory and other test results for severe illness and mortality of COVID-19.

Type of Variable	Type of Study	Author	Total (N)	Severe Illness (N)	Type of Estimate Effect	Effect Estimate (95% CI)	Risk of Bias
Elevated D-dimer per 1 mg/L	Observational	Zhang (a)[32]	48	N/R	HR	1.103 (1.03 to 1.18)	High
D-dimer > 0.5 vs ≤0.5 mg/L	Observational	Zhou[33]	100	6	OR	2.14 (0.21 to 21.39)	Low
D-dimer > 1 vs ≤0.5 mg/L	Observational	Zhou[33]	127	44	OR	18.42 (2.64 to 128.55)	Low
Bacterial Infectionf	Observational	Wang[6]	339	49	HR	1.517 (0.77 to 3.24)	High
PCT >0.5 vs ≤0.5 µmol/L	Observational	Barrasa[26]	46	4	HR	2.7 (0.50 to 13.50)	High
PCT >1 vs ≤1 µmol/L	Observational	Barrasa[26]	46	2	HR	2.4 (0.30 to 20.90)	High

nt-proBNP: N-terminal (NT)-pro hormone BNP
[a] There are 3 included studies with endpoint of mortality
[b] Cycle threshold (Ct) value data of real-time PCR (RT-PCR)
[c] Acute cardiac injury was defined as cardiac injury was defined if the serum level of cardiac troponin I (cTnI) was above the 99th percentile upper reference limit (Wang), regardless of new abnormalities in electrocardiography and echocardiography (Shi)
[d] Cardiac insufficiency was defined when the serum level of NT-pro BNP exceeded the normal range and the presence of associated symptoms, such as dyspnea, orthopnea and edema of lower extremity
[e] The stage of AKI was determined using the peak serum creatinine level after AKI detection, with increases of 1.5 to 1.9, 2.0 to 2.9, and 3 times baseline being defined as AKI stage 1, 2, and 3, respectively (definition by KDIGO)
fBacterial infection was defined as an increased in PCT (the normal range is <0.1 µmol/L.

higher serum lactate dehydrogenase (LDH) (≥250 U/L) and low lymphocyte count (≤1.0 x 10^9/L) with severe illness, with HR 9.80 (95% CI 2.80–33.80) and 3.70 (95% CI 1.80–7.80), respectively.[22] One SR/MA with high risk of bias reported that increased PCT (≥0.50 µmol/L) was associated with severe illness.

Several studies reported an association between higher serum D-dimer levels and both outcomes with variable cut-off points.[22,33] An observational study related to mortality reported serum D-dimer >1 mg/L with OR 18.42 (95% CI 2.64–128.55).33 Low CD3+ CD8+ cell count, ≤75 cell/µL, was reported to be associated with mortality with OR 5.00 (95% CI 1.32–18.96; low risk of bias).29 Another finding associated with mortality was tertile 3 NLR (4.85–88.09) with OR 16.61 (95% CI 1.58–174.66).[30]

Acute cardiac injury was defined by various indicators, including hs-TropI and myoglobin. There were varying results among studies related to acute cardiac injury.[6,7,28,29,32] Only one in five studies reporting the acute cardiac injury marker high-sensitive Troponin I (hs-TnI) showed an association with mortality, with OR 7.20 (95% CI 1.52–34.14).[29] Studies of cardiac insufficiency (defined as serum levels of nt-proBNP exceeding the normal range with symptoms of acute heart failure) as well as studies on its marker alone (nt-proBNP), showed no association between acute heart failure and risk of mortality.[6,7] On the other hand, an observational study with low risk of bias showed an association between COVID-19 patients with kidney-related conditions on admission, including acute kidney injury (stage 2–3), proteinuria, haematuria , peak serum creatinine >13.26 µmol/L, and risk of mortality.[27] We also found a study reporting an association between ARDS and mortality of COVID-19 patients with OR 29.332 (95% CI 12.36–69.58).[6]

DISCUSSION

Age >60 years, hypertension, coronary heart disease, and DM are the risk factors for severe illness of COVID-19.15,22 Laboratory test results associated with severe illness include serum LDH 250–500 U/L, serum LDH >500 U/L, and lymphopenia (lymphocyte count ≤1.0 x 10^9/L).[22] On the other hand, laboratory test results associated with mortality include a CD3+ CD8+ cell count ≤75 cell/µL,[29] D-dimer >1 vs ≤0.5 mg/L,(33) AKI stage 2, AKI stage 3, proteinuria

≥1+, haematuria ≥1+, and peak serum creatinine >13.26 μmol/L.27 The role of other reported risk factors for both severe illness and mortality is mostly supported by insufficient evidence.

Age >60 years is a risk factor for severe illness of COVID-19, supported by an observational study with low risk of bias.[22] The pattern of increasing severe illness of SARS-CoV-2 infection with age is consistent with the epidemiology of MERS-CoV and SARS-CoV-1.[35] In general, there is a progressive decline in immunological competence as one ages.[36] Older people are more likely to develop a dysfunctional immune response resulting in pathological conditions as well as the failure to eradicate pathogens. The ageing lung microenvironment leads to an alteration of dendritic cell maturation and migration of cells to the lymphoid organs. Dysfunction of dendritic cells in turn causes a defective activation of T-cells.[35] Patients with immune dysfunction may generally have a heightened risk of immunologic failure in the initial phase of clinical SARS-CoV-2 infection, followed by a hyperinflammation phase instead of recovery from the disease.[37] From an endocrinological perspective, older people have decreased levels of oestrogens and androgens, which provides an alternative explanation for the link between older age and greater severe illness and mortality in COVID-19. Testosterone is important for the downregulation of inflammation. It has been hypothesised to play a role in the cascade of events resulting in the progression of COVID-19 infection due to cytokine storm. In addition, normal serum testosterone levels have a protective role for several respiratory outcomes. In contrast, low testosterone levels result in reduced respiratory muscle activity and overall diminished exercise capacity and strength.[38]

Based on sufficient evidence, hypertension is a risk factor for severe illness of COVID-19 patients.[15] The link between hypertension and disease outcome is possibly explained by T cell dysfunction observed in patients with hypertension in general. As a result, dysfunctional CD8+ T cells cannot fight against the viral infection and also contribute to overproduction of cytokines.[39] The mechanism of SARS-CoV-1 infection causing reduced ACE2 function and subsequent renin angiotensin system (RAS) dysfunction may also apply to SARS-CoV-2 infection. RAS dysfunction will in turn influence electrolyte and fluid balance as well as blood pressure.[35]

We also suggest a clear link between the presence of coronary heart disease in COVID-19 patients and a threefold increase in risk for severe illness.[4] Interestingly, the presence of cardio-vascular disease affects mortality rate in COVID-19 to a greater extent than a history of COPD, which has not been the case in SARS-CoV-1 infection.44 An acute systemic inflammatory response in COVID-19 patients at the coronary artery level can trigger plaque rupture causing myocardial infarction. Furthermore, several metalloproteinases related to cytokine recruitment and inflammation may mediate the function and effects of ACE2 in atherosclerotic diseases.[48]

Sufficient evidence also supported the role of DM as a risk factor for severe illness.4 In general, diabetic patients are prone to infection due to the impairment of neutrophil chemotaxis and phagocytosis. On the other hand, several specific factors in DM identified in animal and human studies may explain the higher risk for severe illness and mortality in COVID-19, including increased furin, upregulation of ACE2, T cell function impairment, and elevated IL-6 level.40 In addition, IL-6 levels increase over time in severely ill COVID-19 patients requiring intensive care unit (ICU) admission, and IL-6 levels are more elevated in non-survivors compared with survivors.[35] As pancreatic islets express ACE2 receptors, cohort studies of COVID-19 have yet to confirm de novo development of hyperglycaemia/diabetes as seen in patients infected by SARS-CoV-1.[40]

Serum LDH was found to be significantly high in refractory COVID-19 patients.[41] The risk of severe illness was nearly three and ten times higher among COVID-19 patients with serum LDH 250–500 U/L and >500 U/L, respectively.[22] Similarly, a high initial LDH level independently correlates with an adverse clinical outcome of patients with SARS-CoV-1 infection.[42] LDH is essential for pyruvate conversion into lactate in

glucose metabolism. The secretion of LDH is induced by cell membrane necrosis, indicating lung damage or viral infection.[42]

COVID-19 patients with lymphopenia are likely to have an increased risk of severe illness.[22] CD3, as a marker of mature T lymphocytes, helps in the activation of CD4+ T cells and CD8+ T cells.[43] Both CD4+ and CD8+ T cells are critical in controlling influenza virus, SARS-CoV-1, and MERS-CoV infection. Since SARS-CoV-2 is highly homologous to SARS-CoV-1 and MERS-CoV, these types of T cells are hypothesised to play a role in infection control as well.[44] The decline in CD8+ T cell count often precedes radiographic changes in SARS-CoV-1 infection. T cell counts in severe COVID-19 patients are hypothesised to fall progressively through the viraemia phase, acute (pneumonia) phase, and finally in the severe phase of the disease.[37] Thus, it may be important to check for lymphocyte levels early, specifically CD3+ CD8+ T cells and trend the cell count in the COVID-19 disease course to stratify the risk of severe illness and fatality.

Elevated serum D-dimer levels, >1 vs ≤0.5 g/L, may indicate higher risk of death in infected patients.[33] An elevated level of D-dimer signifies a hypercoagulable state in patients with COVID-19.[36] An exceptionally high percentage of aberrant coagulation cases was noticed in severe and critical COVID-19 patients. Such abnormal coagulation was also reported in severe influenza, but it was a rare finding for other coronavirus infections. In the hypothetical pathogenesis of COVID-19, D-dimer levels keep increasing steadily in severely ill patients starting from the initial viraemia phase. The increasing trend may be explained by conjecture. First, direct viral attack in the lung is an important activator of coagulation. Second, dysfunction of endothelial cells in viral infection may result in excess thrombin generation.[37] Third, COVID-19-related hypoxia also stimulates an increase in blood viscosity and hypoxia-inducible transcription factor-dependent signalling pathways.[32] Fourth, certain cytokines, including IL-6, could suppress the fibrinolytic system and activate the coagulation system. In conjunction with the activation of the coagulation system via exposure to tissue factors and other pathways following the viral attack in the lung, these processes may act in a feed-forward manner towards an uncontrolled end-point.[37]

Renal involvement during the course of COVID-19 disease is common[45] and certain degrees of AKI are associated with mortality.[6,27] Studies of AKI in COVID-19 patients in general suggest imprecision of CI.[6] However, if COVID-19 patients are classified as proposed by Cheng and colleagues, stage 2 and stage 3 AKI patients have nearly fourfold and fivefold increased risk of death.[27] Both sepsis- and non-sepsis-related mechanisms may explain AKI in SARS-CoV-2 infection.[46] More studies are needed to provide information related to these mechanisms. The mechanisms leading to acute tubular necrosis (ATN) were hypothesised to be direct viral invasion, cytokine release syndrome, rhabdomyolysis, renal hypoperfusion, cardio-renal syndrome due to viral myocarditis, and hypoxia of renal medulla secondary to alveolar damage.[47] It is plausible that hypercoagulation as a characteristic complication of severe COVID-19 could promote the evolution of ATN becoming irreversible cortical necrosis.[48] The pathological features of renal injury in the setting of COVID-19 include a type of nephrotic syndrome, namely collapsing focal segmental glomerulosclerosis (FSGS) and ATN. Collapsing FSGS is a known complication in patients with another viral infection causing cytopathic effect, namely human immunodeficiency virus (HIV). ACE2 as a SARS-CoV-2 viral entry receptor was also found in podocytes45 and the apical membrane of proximal tubular cells in the kidney.[46] Although PCR result for SARS-CoV-2 in kidney biopsy samples was negative, viral particles were found in the podocytes and proximal tubular cells. This finding suggested the probable involvement of a direct cytopathic effect of SARS-CoV-2 in the development of the kidney injury.[45]

A significant number of patients had proteinuria and a smaller proportion of patients developed haematuria.[46] A proteinuria dipstick test result of 1+ signifies a threefold risk of death, and more massive proteinuria results (2+/3+) indicate a seven times heightened

mortality risk in COVID-19 patients. Similarly, a haematuria test result of 1+ and 2+/3+ indicate a three and nine times higher risk of death, respectively.[27] Both proteinuria and haematuria probably develop from infection-mediated glomerulonephritis.[47]

Collectively, the findings suggest that the worse the AKI, proteinuria, and haematuria each COVID-19 patient has, the higher the risk for mortality may become. Interestingly, in our review, underlying chronic renal failure in COVID-19 patients was not found to be a significant risk factor of COVID-19-related severe illness and death.[7] A single measurement of high serum creatinine level is less valuable in determining the increase in mortality risk.[27] Thus, it may be important to trend the serum creatinine to obtain the peak level and the acute progression of kidney failure. The higher risk of mortality in those with severe AKI, even with renal replacement therapy (RRT), may result from lung–kidney crosstalk in COVID-19 infections.[49] Uncontrolled inflammation in COVID-19 generally could cause multi-organ damage and subsequently bring about organ failure.[35]

Among studies with insufficient evidence, there were two reported conditions, namely ARDS and acute cardiac injury, that we found to have potential association with mortality. ARDS itself may result from a massive pro-inflammatory response,[50] and microthrombotic disease.[51] Direct cardiac injury is theoretically possible since the heart also expresses ACE2. Circulatory failure and myocardial injury observed in several patients may also result from a cytokine storm involving tumour necrosis factor (TNF).[35] Moreover, the dysfunction in cardiac endothelial cells and pericytes due to either direct viral infection or global inflammation in COVID-19 disease course are also hypothesised to cause coronary microcirculatory disruption.[52] Due to insufficient evidence, more high-quality studies are required.

Similarly, the role of a PCT level ≥0.50 g/L as a laboratory test result associated with severe illness was supported by insufficient evidence.[13] In general, viral infection per se attenuates the upregulation of PCT by interferon-alpha release in response to the viral illness. Procalcitonin is actually more specific for bacterial infection and may help to distinguish viral and bacterial infections.[53] Thus, a substantial increase in PCT in COVID-19 patients indicates bacterial coinfection in those developing severe infection.[13] Such a phenomenon is also seen in bacterial coinfections in paediatric patients with viral lower respiratory tract infections, whose infectious causes include coronavirus.[54] More high-quality studies are required to support the significance of an elevated PCT level.

After considering relevant evidence and conjectures, we propose a concise hypothesis of the COVID-19 disease course leading to severe illness and death (**Figure 2**). Concurrent bacterial infection may bring about severe illness in

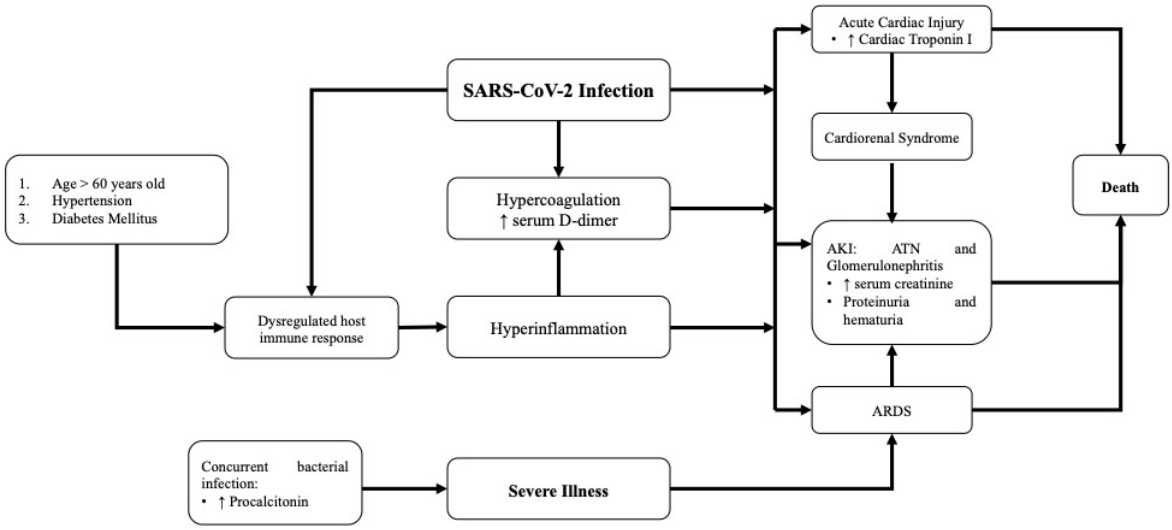

Figure 2. Hypothesis model of COVID-19 disease course leading to severe illness and death.

COVID-19 patients. People aged ≥60 years, with hypertension or with DM have an underlying dysregulation of the immune system. Patients with immune dysfunction may generally have a heightened risk for failure in the initial phase of the clinical course of SARS-CoV-2 infection, followed by a hyperinflammation phase. Both direct viral attack in the lung and inflammation will in turn cause hypercoagulation as shown by elevated serum D-dimer levels. Inflammation and hypercoagulation, together with the hypothesised direct viral infection in lung, heart, and kidney cells, may then lead to ARDS and acute cardiac injury, as well as AKI related to ATN and glomerulonephritis, respectively. Hypercoagulation, hyperinflammation, and/or organ failure(s) play a crucial role in causing death of COVID-19 patients.

Limitations

To date, we believe that our study is the only review collecting and summarising both SR/MA and observational studies and using a systematic approach. However, we also acknowledge the limitations of this review. First, since the evidence pertaining to COVID-19 is growing rapidly, the data collected in this review were restricted to early April 2020. This limitation may impact the collection of data from certain regions in the world in the early period of the pandemic. Second, we may not have retrieved all the existing studies due to our search restriction on studies published in English. To overcome these limitations, we plan to regularly update our review by utilising more robust and comprehensive methods in retrieving all relevant existing studies. Lastly, we also included journal pre-proofs from medRxiv that have not been peer reviewed. However, we carefully appraised all included studies with appropriate quality assessment tools.

In this review, there was only one meta-analysis with low risk of bias. The insufficient evidence is mainly caused by high risk of bias of the available meta-analyses and the lack of meta-analysis of studies related to certain risk factors. Wide CI was in part due to the small sample sizes of the studies. We also found insufficient information in several cohort studies in terms of duration of observational period and time of sample collection.

CONCLUSION

Age >60 years, hypertension, coronary heart disease, and DM are the risk factors for severe illness of COVID-19. Laboratory test results associated with severe illness are serum LDH 250–500 U/L, serum LDH >500 U/L, and lymphopenia (lymphocyte count ≤1.0 x 10^9/L). Test results associated with mortality are CD3+ CD8+ cell count ≤75 cells/μL, D-dimer >1 vs ≤0.5 mg/L, AKI stage 2, AKI stage 3, proteinuria ≥1+, haematuria ≥1+, and peak serum creatinine >13.26 μmol/L. It is crucial to regularly update the review by utilising more robust and comprehensive methods in retrieving all relevant existing studies. Future studies need to specify the duration of observational period and time of sample collection with a larger sample size.

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CONFLICT OF INTEREST

All authors declare no competing interests, other than the research grant.

AUTHOR CONTRIBUTIONS

SS, EDS, RWR, SRFS, MKA and JM contributed equally in drafting the protocol, selecting studies for inclusion, extracting data, assessing risk of bias, carrying out and interpreting the analysis. Both SS and KH contributed in carrying out and interpreting the analysis and providing clinical expertise in the study. Both YP and WW contributed equally in developing the search strategy and running the search and selecting studies for inclusion. YP also contributed in data extraction and assessed the risk of bias. All authors have read and approved the manuscript.

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REFERENCES

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. 2020 [cited 2020 Aug 12). Available from: https://covid19.who.int/
2. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. Am J Respir Crit Care Med. 2020.
3. Gibson PG. The Medical Journal of Australia – Preprint – 24 April 2020 The Medical Journal of Australia – Preprint – 24 April 2020. Med J Aust. 2020;(April).
4. Matsushita K, Ding N, Kou M, et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. medRxiv. 2020.
5. Jain V, Yuan J-M. PREPRINT: Systematic review and meta-analysis of predictive symptoms and comorbidities for severe COVID-19 infection. medRxiv. 2020.
6. 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):639–45.
7. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020.
8. National Institute for Health Research. Risk factors and laboratory test results associated with severe illness and mortality in COVID-19 patients: A rapid review [Internet]. 2020 May 12. 2020 [cited 2020 Jun 30). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=185424.
9. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA - J Am Med Assoc. 2012;307(23):2526–33.
10. Whiting P, Savović J, Higgins JPT, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225–34.
11. Wells G, Shea B, O'Connell D, Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON: Ottawa Hospital Research Institute. 2000.
12. Moher D, Liberati A, Tetzlaff J AD. PRISMA 2009 Flow Diagram. Prism statement. 2009;339.
13. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020;505:190–1.
14. Alqahtani JS, Oyelade T, Aldhahir AM, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis. PLoS ONE. 2020. p. 1–13.
15. Chen Y, Gong X, Wang L, Guo J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. medRxiv [Internet). 2020 Jan 1;2020.03.25.20043133. Available from: http://medrxiv.org/content/early/2020/03/30/2020.03.25.20043133.abstract.
16. Lippi G, Wong J, Henry BM. Hypertension in patients with coronavirus disease 2019 (COVID-19): A pooled analysis. Polish Arch Intern Med. 2020;130(4):304–9.
17. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020;506:145–8.
18. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol. 2020;127.
19. Ma K-L, Liu Z-H, Cao C, et al. COVID-19 myocarditis and severity factors: An adult cohort study. medRxiv [Internet). 2020 Jan 1;2020.03.19.20034124. Available from: http://medrxiv.org/content/early/2020/03/23/2020.03.19.20034124.abstract.
20. Zhou Y, Yang Z, Guo Y, et al. A new predictor of disease severity in patients with COVID-19 in Wuhan, China. medRxiv. 2020.
21. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity. 2020.
22. Ji D, Zhang D, Xu J, et al. Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score. Clin Infect Dis. 2020.
23. Parohan M, Yaghoubi S, Seraj A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality of adult inpatients with Coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of retrospective studies. medRxiv. 2020.
24. Zuin M, Rigatelli G, Zuliani G, Rigatelli A, Mazza A, Roncon L. Arterial hypertension and risk of death in patients with COVID-19 infection: Systematic review and meta-analysis. J Infect. 2020;81(1):e84–6.
25. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–9.
26. Barrasa H, Rello J, Tejada S, et al. SARS-CoV-2 in Spanish intensive care units: Early experience with 15-day survival in Vitoria. Anaesth Crit Care Pain Med. 2020.
27. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829–38.
28. Fu L, Fei J, Xiang H-X, et al. Analysis of death risk

factors among 200 COVID-19 patients in Wuhan, China: A hospital-based case-cohort study. SSRN Electron J. 2020;86(551).
29. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARSCoV- 2: A prospective cohort study. Eur Respir J. 2020;55(5):2000254.
30. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81(1):e6–12.
31. Zhang Y, Cui Y, Shen M, et al. Comorbid diabetes mellitus was associated with poorer prognosis in patients with COVID-19: A retrospective cohort study. medRxiv. 2020.
32. Zhang F, Yang D, Li J, et al. Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: A single center retrospective cohort study. medRxiv. 2020.
33. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
34. Xie J, Hungerford D, Chen H, et al. Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19. SSRN Electron J. 2020.
35. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews Immunology. 2020. p. 1–12.
36. Schulz AR, Mälzer JN, Domingo C, et al. Low thymic activity and dendritic cell numbers are associated with the immune response to primary viral infection in elderly humans. J Immunol. 2015;195(10):4699–711.
37. Cao W, Li T. COVID-19: towards understanding of pathogenesis. Cell Res. 2020;30:367–9.
38. Pozzilli P, Lenzi A. Testosterone, a key hormone in the context of COVID-19 pandemic. Metabolism. 2020;108.
39. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020.
40. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr Clin Res Rev. 2020;14(4):303–10.
41. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 – A systematic review. Life Sci. 2020;254.
42. Tsui PT, Kwok ML, Yuen H, Lai ST. Severe acute respiratory syndrome: Clinical outcome and prognostic correlates. Emerg Infect Dis. 2003;9(9):1064–9.
43. He R, Lu Z, Zhang L, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol. 2020;127.
44. Liu R, Wang Y, Li J, et al. Decreased T cell populations contribute to the increased severity of COVID-19. Clin Chim Acta. 2020;508:110–4.
45. Kissling S, Rotman S, Gerber C, et al. Collapsing glomerulopathy in a COVID-19 patient. Kidney Int. 2020.
46. Soleimani M. Acute kidney injury in SARS-CoV-2 infection: Direct effect of virus on kidney proximal tubule cells. Int J Mol Sci. 2020;21(9):E3275.
47. Hassanein M, Thomas G, Taliercio J. Management of acute kidney injury in COVID-19. Cleve Clin J Med [Internet). 2020 May 20; Available from: http://ccjm.org/content/early/2020/05/13/ccjm.87a.ccc034.abstract.
48. Batlle D, Soler MJ, Sparks MA, et al. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. J Am Soc Nephrol. 2020.
49. Ali H, Daoud A, Mohamed MM, et al. Survival rate in acute kidney injury superimposed COVID-19 patients: a systematic review and meta-analysis. Ren Fail. 2020;42(1):393–7.
50. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215.
51. Chang JC. Acute Respiratory distress syndrome as an organ phenotype of vascular microthrombotic disease: Based on hemostatic theory and endothelial molecular pathogenesis. Clinical and Applied Thrombosis/Hemostasis. 2019.
52. Akhmerov A, Marbán E. COVID-19 and the Heart. Circ Res. 2020;126:1443–55.
53. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: Past, present and future. BMC Med. 2011;9:107.
54. Kotula JJ, Moore WS, Chopra A, Cies JJ. Association of procalcitonin value and bacterial coinfections in pediatric patients with viral lower respiratory tract infections admitted to the Pediatric Intensive Care Unit. J Pediatr Pharmacol Ther. 2018;23(6):466–72.

Factors Associated with Death in COVID-19 Patients in Jakarta, Indonesia: An Epidemiological Study

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ABSTRAK

Latar belakang: *penyakit Coronavirus 2019 adalah penyakit sistem pernapasan yang baru saja muncul dan menjadi pandemi. Indonesia mengalami peningkatan jumlah kasus yang cukup drastis tetapi data lokal terkait hal ini masih jarang didapatkan.* ***Metode:*** *analisis dalam riset ini menggunakan data rekapitulasi Penelusuran Epidemiologi (PE) yang dikeluarkan oleh Pemerintah Daerah Khusus Ibukota Jakarta dari 2 Maret hingga 27 April 2020.* ***Hasil:*** *dari total 4.052 pasien, 381 (9,4%) pasien meninggal. Analisis multivariabel menunjukkan bahwa kematian berhubungan dengan usia tua (odds ratio [OR] 1,03; 95% confidence interval [CI] 1,02, 1,05, peningkatan usia per tahun; p<0,001), sesak napas (OR 4,83; 95% CI 3,20, 7,29; p <0,001), pneumonia (OR 2,46; 95%CI 1,56, 3,88; p<0,001), dan riwayat hipertensi (OR 1,86; 95%CI 1,24, 2,78; p=0,003). Angka kematian tertinggi terjadi pada 6 April 2020 dan menurun di beberapa pekan selanjutnya, setelah pembatasan sosial berskala besar diberlakukan.* ***Kesimpulan:*** *usia tua, sesak napas, pneumonia, dan riwayat hipertensi berhubugan dengan risiko kematian. Mortalitas tergolong tinggi tetapi mungkin dapat dikurangi dengan pembatasan interaksi sosial.*

Kata kunci: *COVID-19, kematian, Indonesia, Jakarta, karakteristik pasien.*

ABSTRACT

Background: *Coronavirus Disease 2019 is an emerging respiratory disease that is now a pandemic. Indonesia is experiencing a rapid surge of cases but the local data are scarce.* ***Methods:*** *this is an analysis using data from the ongoing recapitulation of Epidemiological Surveillance (ES) by the Provincial Health Office of Jakarta from March 2nd to April 27th 2020. We evaluated demographic and clinical characteristics of all confirmed cases in association with death.* ***Results:*** *of the 4,052 patients, 381 (9.4%) patients were deceased. Multivariable analysis showed that death was associated with older age (odds ratio [OR] 1.03; 95% confidence interval [CI] 1.02, 1.05, per year increase; p<0.001), dyspnea (OR 4.83; 95% CI 3.20, 7.29; p<0.001), pneumonia (OR 2.46; 95%CI 1.56, 3.88; p<0.001), and pre-existing hypertension (OR 1.86; 95% CI 1.24, 2.78; p=0.003). Death was*

highest in the week of April 6th 2020 and declined in the subsequent weeks, after a large-scale social restriction commenced. ***Conclusion:*** *older age, dyspnea, pneumonia, and pre-existing hypertension were associated with death. Mortality was high, but may be reduced by lockdown.*

Keywords: *COVID-19, death, Indonesia, Jakarta, patient characteristics.*

INTRODUCTION

Coronavirus Disease 19, or widely known as COVID-19 is a new emerging respiratory disease that can cause respiratory failure due to severe pneumonia.[1] This viral infection was first reported in December 2019 in Wuhan, China and suspected to be transmitted through zoonotic origin, followed by human to human transmission.[2] By May 22nd 2020, a total of 4,993,470 confirmed cases have been reported globally and the disease has spread rapidly throughout at least 215 countries, including Indonesia.[3]

The first two cases in Indonesia were identified in West Java Province on March 2nd 2020.[4] Thenceforth, the number of COVID-19 cases in the country increased remarkably, reaching 20,796 confirmed cases on April 22nd 2020. At the time of preparing this manuscript, the number of COVID-19 cases and mortality rates in Indonesia are still increasing and the end of the epidemic is still uncertain.[5,6] Published reports on the epidemiology and clinical characteristics of COVID-19 cases from Indonesia are scarce. High-quality evidence is important for understanding the disease, improving the quality of care of patients and could serve as a basis for policy making. In this study, we analyze demographic and clinical parameters associated with the mortality of laboratory-confirmed cases with COVID-19 in DKI Jakarta, Indonesia.

METHODS

This is a retrospective cohort study using data from the ongoing recapitulation of Epidemiological Surveillance (ES) conducted by the Provincial Health Office of Capital Special Region of Jakarta (*Dinas Kesehatan/ Dinkes Provinsi DKI Jakarta*).

The laboratory-confirmed patients are defined as patients with a positive result on real-time reverse transcription polymerase chain reaction (RT-PCR) for the presence of SARS-CoV-2 in either the nasal or pharyngeal swab specimens, irrespective of the clinical signs and symptoms. All confirmed cases of COVID-19 in Jakarta between March 2nd 2020 and April 29th 2020 were included in the analysis. This study was approved by The Ethics Committee of Faculty of Medicine University of Indonesia (No: KET-506/ UN2.F1/ETIK/PPM.00.02/2020).

Data collection

Data were collected using Epidemiological Surveillance (Penyelidikan Epidemiologi/PE) forms which were distributed to all healthcare facilities in the province, including all public primary care centres (Puskesmas) and public and private hospitals. Doctors or nurses who provided care for patients suspected with COVID-19 infection were obliged to fill in the PE. The PE forms were later being submitted to Dinkes Provinsi DKI Jakarta.

The PE form consists of questions related to patient demographic characteristics and clinical information. Signs and symptoms that were asked in the questionnaire included body temperature and the presence of fever, cough, cold, sore throat, dyspnea, chills, headache, malaise, myalgia, nausea and emesis, abdominal pain and diarrhea. Other conditions and comorbidities that were asked included the presence history of diabetes, heart disease, hypertension, malignancy, immunologic disorder, chronic kidney failure, chronic liver failure, and chronic obstructive pulmonary disease (COPD). In case patients were hospitalized, the start and end date of hospitalization were recorded together with whether there was admission to the intensive care unit (ICU), intubation performed, and the use of extracorporeal membrane oxygenation (ECMO) machine. The end date of hospitalization was also recorded and data about the clinical outcomes were collected.

Age was classified into 5 groups; 0-9 years, 10-19 years, 20-49 years, 50-69 years, and older than 70 years. Patient's address was classified into 6 groups; including 5 areas of Jakarta (South, West, East, North, and Central) and outside Jakarta if patients had non-Jakarta address. Within subjects with available data of body temperature, we categorized them into 4 groups (<37°C, 37.3–38°C, 38.1– 39°C, and >39°C). The time from the onset of the symptoms to nasal and/or throat swab tests were used as a proxy for patient's access to a health facility with a shorter number represents better access.

Outcome Measures

Death was considered as the main outcome in this study. All deaths that occurred after the diagnosis of COVID-19 were considered to be the consequence of the infection. This clinical outcome was followed up until April 29th 2020.

Data Analysis

Patients' demographic information and clinical characteristics were tabulated for descriptive purposes. All these variables were considered as potential predictors of death during the follow-up time. Univariable regression was first performed to evaluate the unadjusted relation between each predictor and the occurrence of death. We selected the statistically significant predictors from the univariable analysis and evaluated them using multivariable logistic regression.

Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding p values. Statistical significance was considered to be a 2-sided p value <0.05. All analyses were performed using SPSS Version 25.0 for Mac (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 4,052 COVID-19 patients included in the study, 381 (9.4%) patients were deceased, while 3670 (90.6%) patients survived (**Table 1**). Among the surviving patients, 412 (11.2%) patients were cured, 2,012 (54.8%) patients were still hospitalised, and 1,246 (33.6%) patients were in self-isolation.

Table 1 shows the demographic and clinical characteristics of the study population in total and separately for those who died and those who survived. The mean age of the patients was 45.8 years. The majority of the patients were from age groups of 20 to 49 years and 50 to 69 years (51.2% and 37.6% respectively, from the total population). Those who died were significantly older than those who survived. Similarly, analysis by age groups also showed significant differences in the risk of death with more patients in the 50 to 69 years and older than 70 years groups dying. There were more male patients in the total population and among those who died. The majority of the patients had non-Jakarta addresses and death rates were significantly different depending on the area where they lived.

Among all the comorbidities, hypertension was revealed to be the most common disease reported (18.3%), followed by diabetes (11.1%), heart disease (6.9%), and COPD (5.6%). Among 800 patients with the non-missing data on the existence of all comorbidities, 83.6% were reported to having at least one comorbidity. The proportion of patients with hypertension, diabetes, heart disease, and renal diseases were significantly higher in those who died.

Cough (61.0%), fever (53.0%), malaise (32.4%) and dyspnea (30.2%) were the most commonly reported symptoms, while pneumonia occurred in 41.1% of patients. The proportion of patients with these symptoms and pneumonia was also significantly higher among those who died. Within 655 patients with reported body temperature, the majority had a body temperature between 37.3 – 38.0°C.

The mean duration between symptom onset and swab test in the total population was 7 days (SD 6.0) and was significantly different between those who died and those who survived (9.9 days vs 8 days, $p < 0.001$). The following procedures were also more common in those who died as compared to those who survived; ICU admission (20 [16.0%] vs 17 [1.2%], $p < 0.001$), intubation (17 [13.8%] vs 11 [0.8%], $p < 0.001$), and ECMO (7 [5.9%] vs 4 [0.3%], $p < 0.001$).

In **Table 2**, we show that in the univariable analysis, older age, being older than 70 years, male, residing in Central or South Jakarta, having symptoms of cough, fever, malaise, dyspnea,

Table 1. Baseline characteristics of the patients.

Characteristics	Total (n=4052)	Death	
		Yes (n=381)	No (n=3670)
Age (n=3986)	45.8 (16.3)	58.2 (14.3)	44.5 (15.9)
Age group			
- 0 to 9 years	47 (1.2)	4 (1.1)	43 (1.2)
- 10 to 19 years	133 (3.3)	2 (0.5)	131 (3.6)
- 20 to 49 years	2040 (51.2)	69 (18.4)	1971 (54.6)
- 50 to 69 years	1497 (37.6)	220 (58.5)	1277 (35.4)
- Older than 70 years	269 (6.8)	81 (21.5)	188 (5.2)
Sex (n=4043), male	2169 (53.5)	256 (67.5)	1913 (52.2)
Registered address (n=3657)			
- West Jakarta	571 (14.1)	51 (13.4)	520 (14.2)
- Central Jakarta	554 (13.7)	57 (15.0)	497 (13.5)
- South Jakarta	627 (15.5)	88 (23.1)	539 (14.7)
- East Jakarta	666 (16.4)	81 (21.3)	585 (16.0)
- North Jakarta	459 (11.3)	41 (10.8)	418 (11.4)
- Outside Jakarta	1161 (28.7)	63 (16.5)	1098 (30.0)
Citizenship (n=4051)			
- Indonesian	3915 (96.6)	374 (98.2)	3541 (96.5)
- Foreigner	136 (3.4)	7 (1.8)	129 (3.5)
Symptoms			
- Cough (n=2258)	1377 (61.0)	184 (81.8)	1193 (58.7)
- Fever (n=2242)	1189 (53.0)	167 (74.6)	1022 (50.6)
- Malaise (n=2123)	688 (32.4)	115 (57.2)	573 (29.8)
- Dyspnea (n=2255)	682 (30.2)	167 (74.2)	515 (25.4)
- Headache (n=2128)	483 (22.7)	61 (30.5)	422 (21.9)
- Nausea/emesis (n=2058)	434 (21.1)	57 (29.7)	377 (20.2)
- Sore throat (n=2256)	508 (22.5)	71 (31.7)	437 (21.5)
- Cold/runny nose (n=2255)	507 (22.5)	49 (21.7)	458 (22.6)
- Myalgia (n=2087)	360 (17.2)	41 (21.2)	319 (16.8)
- Chills (n=2081)	231 (11.1)	40 (20.6)	191 (10.1)
- Abdominal pain (n=2069)	145 (7.0)	19 (9.9)	126 (6.7)
- Diarrhea (n=2126)	170 (8.0)	21 (10.6)	149 (7.7)
- Pneumonia (n=2077)	853 (41.1)	182 (81.6)	671 (36.2)
Temperature (n=655)			
- < 37.3 ºC	194 (29.6)	14 (16.7)	180 (31.5)
- 37.3 – 38.0 ºC	273 (41.7)	37 (44.0)	236 (41.3)
- 38.1 – 39.0 ºC	158 (24.1)	26 (31.0)	132 (23.1)
- >39.0 ºC	30 (4.6)	7 (8.3)	23 (4.0)
Existing comorbidity (n=800)	669 (83.6)	153 (92.7)	516 (81.3)
Comorbidities			
- Hypertension (n=2131)	390 (18.3)	106 (47.5)	284 (14.9)
- COPD (n=2229)	125 (5.6)	14 (6.2)	111 (5.5)
- Diabetes (n=2131)	236 (11.1)	66 (29.5)	170 (8.9)
- Heart disease (n=2131)	148 (6.9)	49 (22.0)	99 (5.2)
- Renal disease (n=2129)	37 (0.9)	19 (8.5)	18 (0.9)
- Malignancy (n=2131)	8 (0.2)	2 (0.9)	6 (0.3)
- Immunological disorder (n=2132)	14 (0.3)	4 (1.8)	10 (0.5)
- Liver failure (n=2126)	5 (0.1)	2 (0.9)	3 (0.2)
- Obesity	5 (0.1)	0 (0.0)	5 (3.2)

Values are means with standard deviations in for continuous variables and n (%) for frequencies. In case skewed data (*), the median with the interquartile range is presented. COPD = chronic obstructive pulmonary disease.

Table 2. Factors associated with death in patients with laboratory confirmed COVID-19

Variable	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.06 (1.05; 1.07)	<0.001	1.03 (1.02; 1.05)	<0.001
Age group				
- 0 to 9 years	Reference			
- 10 to 19 years	0.16 (0.03; 0.93)	0.041		
- 20 to 49 years	0.38 (0.13; 1.08)	0.069		
- 50 to 69 years	1.85 (0.66; 5.21)	0.243		
- Older than 70 years	4.63 (1.61; 13.33)	0.004		
Sex, male	1.91 (1.52; 2.39)	<0.001	1.17 (0.80, 1.70)	0.42
Registered address				
- West Jakarta	1.17 (0.79, 1.74)	0.44	1.03 (0.54, 1.97)	0.92
- Central Jakarta	1.67 (1.16, 2.40)	0.006	0.87 (0.47, 1.61)	0.66
- South Jakarta	1.41 (0.98, 2.04)	0.07	0.99 (0.53, 1.82)	0.96
- East Jakarta	1.00 (0.65, 1.54)	1.00	1.04 (0.54, 1.98)	0.92
- North Jakarta	0.59 (0.40, 0.86)	0.006	0.93 (0.49, 1.79)	0.83
- Outside Jakarta	Reference		Reference	
Citizenship, foreigner	0.51 (0.24; 1.11)	0.09		
Symptoms				
- Cough	3.16 (2.23; 4.48)	<0.001	1.01 (0.62; 1.63)	0.98
- Fever	2.86 (2.09; 3.91)	<0.001	1.26 (0.83; 1.93)	0.28
- Malaise	3.15 (2.34; 4.23)	<0.001	1.04 (0.67; 1.59)	0.88
- Dyspnea	8.47 (6.18; 11.61)	<0.001	4.83 (3.20; 7.29)	<0.001
- Headache	1.57 (1.14; 2.16)	0.006	1.09 (0.71; 1.67)	0.71
- Nausea/emesis	1.67 (1.20; 2.32)	0.002	0.79 (0.52; 1.21)	0.28
- Sore throat	1.69 (1.25; 2.29)	0.001	1.00 (0.66; 1.51)	0.98
- Cold/runny nose	0.95 (0.68; 1.32)	0.95		
- Myalgia	1.33 (0.92; 1.92)	0.13		
- Chills	2.31 (1.58; 3.37)	<0.001	1.02 (0.62; 1.69)	0.95
- Abdominal pain	1.53 (0.92; 2.53)	0.10		
- Diarrhea	1.41 (0.87; 2.28)	0.16		
- Pneumonia	7.83 (5.05; 11.13)	<0.001	2.46 (1.56; 3.88)	<0.001
Temperature				
- < 37.3 °C	Reference			
- 37.3 – 38.0 °C	2.12 (1.06; 3.84))	0.03		
- 38.1 – 39.0 °C	2.53 (1.27; 5.04)	0.008		
- >39.0 °C	3.92 (1.43; 10.70)	0.008		
Existing comorbidity, yes	2.94 (1.58; 5.47)	0.001		
Comorbidity				
- Hypertension	5.18 (3.87; 6.93)	<0.001	1.86 (1.24; 2.78)	0.003
- COPD	1.12 (0.63; 1.99)	0.70		
- Diabetes	4.27 (3.08; 5.92)	<0.001	1.26 (0.80; 1.98)	0.32
- Heart disease	5.15 (3.53; 7.50)	<0.001	1.43 (0.85; 2.41)	0.18
- Renal disease	9.77 (5.05; 18.91)	<0.001	2.42 (0.99; 5.95)	0.06
- Malignancy	2.87 (0.58; 14.30)	0.20		
- Immunological disorder	3.47 (1.08; 11.15)	0.04	2.63 (0.44; 15.77)	0.29
- Liver failure	5.76 (0.96; 34.66)	0.06		
- Obesity	a			

Data are presented as OR from (univariable or multivariable) logistic regression coefficients with 95% confidence intervals for every one-unit increase in the predictor or for positive predictor. COPD = chronic obstructive pulmonary disease. aThe number of cases was too small to enable analysis.

headache, nausea/emesis, sore throat, chills, and pneumonia were significantly associated with a higher risk of death. Deaths were also more likely with higher body temperature, pre-existing comorbidities (mainly hypertension, diabetes, heart disease, renal disease, and immunological disorder).

When all significant demographic and clinical characteristics ($p < 0.05$) were included in the multivariable analysis, we show that most associations between these characteristics and the occurrence of deaths became non-significant. The characteristics which remained significantly associated with higher mortality were older age (OR 1.03, one year increment), dyspnea (OR 4.83), evidence of pneumonia (OR 2.46), and pre-existing hypertension (OR 1.86).

Based on the total number of deaths and confirmed cases, the case fatality rate (CFR) in Jakarta was estimated to be 9.4%. The number of confirmed cases and death due to COVID-19 showed an increased surge during the observation period. The weekly number of new confirmed cases was consistently increasing during the observation period (**Figure 1**). The weekly number of deaths, on the other hand, reached its peak in the week of April 6th 2020 and dropped in the following weeks. This is as shown in **Figure 2** where the slope becomes less steep in the following weeks after April 6th 2020.

DISCUSSION

In the present study we provided evidence suggesting that among laboratory-confirmed cases of COVID-19 in Jakarta, the odds of death were greater if patients were older, had dyspnea, pneumonia, and pre-existing hypertension.

To the best of our knowledge, this is the

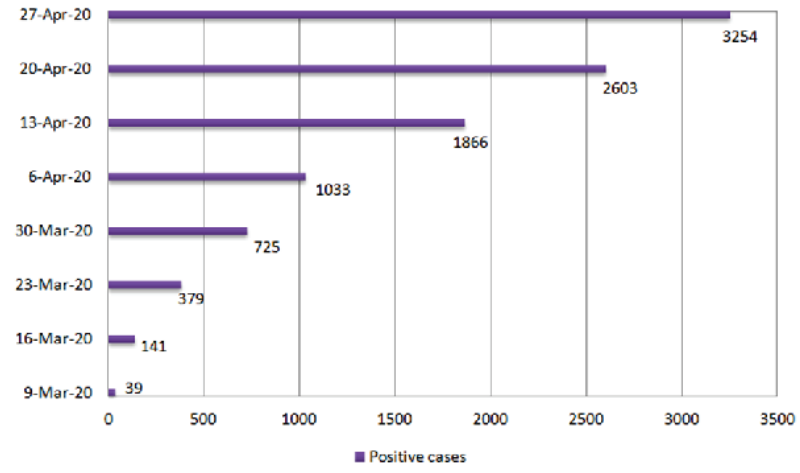

Figure 1. Weekly cumulative number of COVID-19 cases in Jakarta, Indonesia.

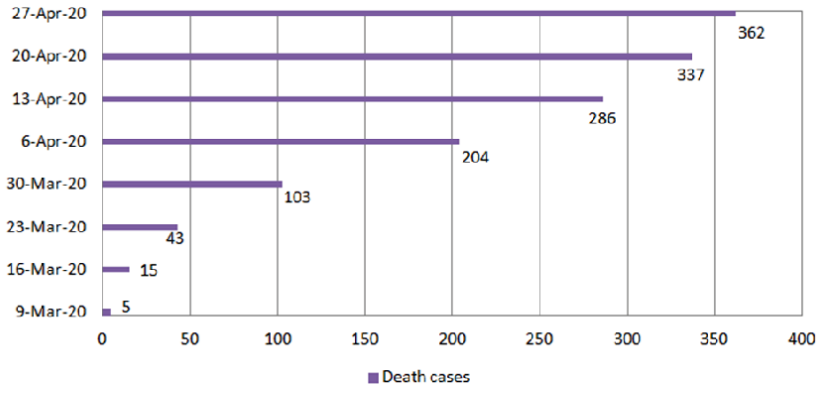

Figure 2. Weekly cumulative number of deaths in patients with COVID-19 in Jakarta, Indonesia.

first and largest analysis using epidemiological surveillance data to assess risk factors for mortality in laboratory-confirmed COVID-19 patients in Indonesia. The study population was comprised of people living in the epicenter of local transmissions, the urban setting of Jakarta and its surrounding area (Jabodetabek) with relatively good access to the healthcare facility. In terms of time, this study captured the initial phase of the epidemic in Indonesia (within 2 months after the first case of COVID-19 in Indonesia was reported). The data comprising the entire population with laboratory confirmed COVID-19 in the area were included in the analysis.

Our finding that older age was related with higher mortality in COVID-19 patients is in concordance with several previous studies.[7,8] Mortality was higher by 10% per year increase in these studies as compared to 3% in the present study. This difference might be attributed to the fact that only adult patients were included in the previous study. Our finding also confirms previous studies that showed significant increased risk of death in patients aged >65 years.[9,10] Due to impaired immune response, older patients tend to have a more serious condition and poorer response to treatments.

Pneumonia and dyspnea (shortness of breath) have been reported to be associated with death in the previous studies.[11,12] The latter was associated with the occurrence of acute respiratory distress syndrome (ARDS) in COVID-19 patients.[8] In addition, an earlier study also revealed that early onset of dyspnea may be a marker of poor prognosis.[11] These findings are also supported by a meta-analysis which suggested that patients with dyspnea showed worse clinical outcomes.[12] In the present study a total of 41% patients were reported with pneumonia and 30% had dyspnea. The proportions are higher than in China where less than 20% confirmed cases had pneumonia and only 14% had dyspnea.[13]

This study revealed pre-existing hypertension was independently associated with mortality in COVID-19 patients in Jakarta. Earlier studies also reported that hypertension was the most common underlying disease of the COVID-19 patients, especially in fatal cases.[8,11,14] Disruption of the renin-angiotensin system may explain this phenomenon.[15] It is postulated that pre-existing cardiovascular disease, including hypertension, contributes to the occurrence of pneumonia and fatal symptoms in COVID-19.[16] Our analysis showed that COVID-19 patients with pre-existing hypertension have an approximately 2-fold risk of death as compared to patients without. This is relatively comparable to the increased risk of developing severe COVID-19 (OR:2.92) estimated by a large meta-analysis from China.[17]

The unadjusted analyses showed that diabetes increased risk of death in COVID-19 patients but this association became non-significant after adjustment for other characteristics (age, sex, symptoms, and other comorbidities). This finding suggests that diabetes itself may not have direct implication on infection severity, but rather present coexisting with other worsening factors such as older age and hypertension. This is in line with previous studies which showed no significant association between diabetes and mortality of COVID-19 patients when other factors such as age, sex, other comorbidities were taken into account in the analyses.[18,19]

We showed a case fatality rate (CFR) of 9.4% in our study population, which was among the highest in the world. This rate leads among countries in Southeast Asia, higher than in Wuhan, China (4.3% of confirmed cases) and is almost twice the global mortality rate of 5.97%.[20,21] The high CFR in our population might partially be explained by the limited capacity of PCR testing which resulted in serious under-reporting.[22] It is estimated that only 0.03 tests were done daily per thousand people.20 Patients with more pronounced symptoms and therefore a more severe condition were more likely to seek help and therefore had better access to PCR tests. Nonetheless, the high CFR might also reflect poorer healthcare capacity in responding to the epidemic. Data from the Provincial Health Office of Special Capital Region of Jakarta revealed the death cases during February 2020 were 5792 people, markedly increased from January 2020 (3072 deaths).[23] This might indicate undetected deaths related to COVID-19 before the first case was diagnosed in Indonesia.

About one third of patients in this study had a registered address outside Jakarta. This finding might indicate the urban problem of Jakarta and public health problems. Many people possibly work and live in Jakarta while still maintaining their "outside Jakarta" address on their ID card. Additionally, people who live in the surrounding areas near Jakarta might prefer to go to Jakarta when seeking medical services. Therefore, basing the calculation of healthcare services demand solely on the number of Jakarta inhabitants would result in serious overestimation of Jakarta's preparedness for the pandemic.

A large-scale social restriction (pembatasan sosial berskala besar or PSBB) has been imposed in Jakarta since April 10th 2020.[24] The PSBB in Jakarta seems to create an impact in reducing the curve slope of both the cumulative number of confirmed cases and the number of deaths (**Figure 1** and **2**). The number of weekly new confirmed cases dropped to 651 patients in the period between April 20th and April 26th 2020, 10 days after PSBB was applied. This number was lower than in the previous weeks and in the early days of PSBB (833 patients between April 6th – April 13th 2020). In line with this, the number of weekly death cases dropped to 25 patients in the period between April 20th and April 26th 2020. This number was lower than in the previous weeks and in the early days of PSBB (82 patients between 6 April – 13 April 2020). These results are preliminary but indicate the effectiveness of the large-scale social restriction in controlling the spread and mitigating the catastrophe of COVID-19. The mathematical modeling suggested that quarantine, school closure and social distancing had an impact in the reduction of COVID-19 cases.[25,26] India, which adopted early social distancing and social lockdown had lower mortality (3%) due to COVID-19 compared to Spain (12%) and France (19.9%).[3,27] Australia experienced success in decreasing the rate of COVID-19 cases together with low mortality rate (1.4% per 10 May 2020) as an impact of international travel restrictions and social distancing.[28]

This study has several limitations. First, no data were available regarding the diagnostic and treatment received by the patients. Diagnostic and therapeutic measures, notably, may have a significant role in modifying the clinical course of the disease and its outcomes. Laboratory and radiologic findings may provide insights into the course of the disease and severity of the condition. In the absence of such information, interpretation of our findings needs to be done with caution. Secondly, some information in the PE form was missing because it was left empty by the interviewer. Proper training of the healthcare providers might increase the quality of the PE form database.

CONCLUSION

We identified older age, dyspnea, pneumonia, and pre-existing hypertension as predictors for mortality among the laboratory confirmed cases of COVID-19 in DKI Jakarta, Indonesia. The mortality rate was high at 9.4%. The research has also shown the apparent beneficial impact of PSBB in reducing the spread of COVID-19.

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REFERENCES

1. Ceraolo C, Giorgi FM. Genomic variance of the 2019 nCoV coronavirus. Med Virol. 2020;92(5):522–8.
2. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel Coronavirus–infected pneumonia. N Engl J Med. 2020;382(13):1199–207.
3. World Health Organization. Coronavirus disease (COVID-19) Situation Report 22 May 2020. (May):1–18. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200522-covid-19-sitrep-123.pdf?sfvrsn=5ad1bc3_4.
4. Ministry of Health Republic of Indonesia. Dua pasien positif Covid-19 dirawat di RSPI Sulianti Saroso. https://www.kemkes.go.id/article/view/20030200009/dua-pasien-positif-covid-19-dirawat-di-rspi-sulianti-saroso.html (2020, accessed May 25, 2020).
5. Setiati S, Azwar MK. COVID-19 and Indonesia. Acta Med Indones. 2020;52(1):84–9.
6. Ministry of Health Republic of Indonesia. Situasi terkini perkembangan novel Coronavirus (COVID-19) - 22 Mei 2020. https://covid19.kemkes.go.id/situasi-infeksi-emerging/info-corona-virus/situasi-terkini-

perkembangan-coronavirus-disease-covid-19-23-mei-2020/#.XsvE9GhKjIU (2020).
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
8. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;E1–E10.
9. Du R, Liang L, Yang C, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS- CoV-2 : a prospective cohort study. Eur Respir J. 2020;56(1):1–8.
10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective , observational study. Lancet Respir Med. 2020;8(5):475–81.
11. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. Am J Respir Crit Care Med. 2020;201(11):1372–9.
12. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81(2):e16–e25.
13. Wu Z, Jennifer M. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42.
14. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):P507-513.
15. Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system? a call for epidemiologic investigations. Clin Infect Dis. 2020;71(15):870–4.
16. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17(5):259–60.
17. Wang X, Fang X, Cai Z, et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: A systemic review and meta-analysis. Am Assoc Adv Sci. 2020;1–16.
18. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: Prospective observational cohort study. BMJ. 2020;369(m1985):1–12.
19. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369(m1966):1–15.
20. Hasell J, Mathieu E, Beltekian D, et al. Coronavirus (COVID-19) testing statistics and research. https://ourworldindata.org/coronavirus-testing#indonesiaaccessed (2020).
21. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. J Am Med Assoc. 2020;323(11):1061–9.
22. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health care resource availability. Lancet Glob Heal. 2020;8(4):e480.
23. Statistical Unit Special Capital Region of Jakarta. Pelaporan Kematian Periode Januari-Desember 2019 dan Januari-April 2020 di Provinsi DKI Jakarta. http://statistik.jakarta.go.id/pelaporan-kematian-periode-januari-desember-2019-dan-januari-april-2020-di-provinsi-dki-jakarta/ (2020).
24. Provincial Health Office of Special Capital Region of Jakarta. Poin penting PSBB di DKI Jakarta. (April): https://corona.jakarta.go.id/id/publikasi (2020).
25. Lewnard J, Co N. Scientific and ethical basis for social-distancing interventions against COVID-19. Lancet Infect Dis. 2020;20(6):631–3.
26. Stein RA. COVID-19 and rationally layered social distancing. Int J Clin Pract. 2020;14(00):e13501.
27. Paital B, Das K, Kumar S. Science of the Total Environment Inter nation social lockdown versus medical care against COVID-19, a mild environmental insight with special reference to India. Sci Total Environ. 2020;728(138914):1–18.
28. COVID-19 National Incident Room Surveillance Team. COVID-19, Australia: Epidemiology Report 15. 2020. p. 1–26.

Effect of Antimuscarinic Drugs on Cognitive Functions in the Management of Overactive Bladder in Elderly

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ABSTRAK

Latar belakang: *overactive bladder (OAB) terjadi pada sekitar 17-41% pada lansia di lingkungan tempat tinggal komunitas. Selama beberapa tahun, antimuskarinik telah divalidasi sebagai pilihan pertama untuk tata laksana OAB. Meskipun banyak data yang diperoleh dari uji klinis terkait penggunaan antimuskarinik. Penelitian terkait efek samping dari obat antimuskarinik terhadap fungsi kognitif pada lansia masih jarang dilakukan. Tujuan dari penelitian ini adalah untuk mengetahui efek dari terapi antimuskarinik terhadap fungsi kognitif pada pasien lanjut usia dengan OAB.* ***Metode:*** *desain penelitian ini adalah tinjauan sistematis dan meta-analisis. Studi dikumpulkan menggunakan beberapa mesin pencari; diantaranya adalah PubMed, Science Direct, Cochrane, and EBSCOhost menggunakan kata kunci MeSH yang sudah ditentukan sebelumnya dengan operator Boolean. Pemilihan studi dilakukan oleh 3 pengulas. Seluruh studi yang memenuhi kriteria inklusi selanjutnya melalui proses review full-text. Untuk setiap artikel full-text yang terpilih, ekstraksi data dilakukan pada data: demografis pasien, tipe antimuskarinik yang digunakan, placebo, dosis, follow-up, dan skor total Mini Mental State Examination(MMSE).* ***Hasil:*** *total sebanyak 8 studi yang terpilih dari 146 publikasi yang ada sebelumnya. Terdapat 8 jenis antimuskarinik yang dievaluasi dari studi-studi yang ada, yaitu: Oksibutinin, Darifenacin, Tolterodin, Trospium, Imidafenacin, Propiverin hidroklorida, Fesoterodin, dan Solifenacin. Oksibutinin menunjukkan efek yang paling besar pada penurunan skor MMSE [Perbedaan rerata: -2,90; 95% CI: -4,07, -1,73]. Darifenacin dan Tolterodin juga menunjukkan penurunan yang signifikan pada skor total MMSE, namun lebih inferior daripada Oksibutinin.* ***Kesimpulan:*** *penggunaan obat-obatan antimuskarinik hanya memiliki efek yang minimal terhadap fungsi kognitif dalam penanganan OAB pada pasien usia lanjut. Akan tetapi, Oksibutinin, Darifenacin, dan Tolterodin menunjukkan penurunan yang signifikan terhadap fungsi kognitif, ditunjukkan dari penurunan total skor MMSE.*

Keywords: *obat antimuskarinik, fungsi kognitif, overactive bladder, mini-mental state examination (MMSE).*

ABSTRACT

Background: *overactive bladder (OAB) affects 17-41% older adults in community dwelled setting. For several years, antimuscarinics have been validated as the first-line medical treatment for OAB. Despite abundant data obtained from clinical trials provisions the use of antimuscarinics, investigation about the effect of this drug on cognitive function in elderly remains scarce. The objective of this study is to investigate the effect of antimuscarinics therapy on cognitive functions in OAB geriatric patients.* ***Methods:*** *this study design is a systematic review and meta-analysis. Studies were collected using several search engines; those were PubMed, Science Direct, Cochrane, and EBSCOhost using predetermined MeSH keywords with Boolean operators. Selection of studies was done by three reviewers. Studies which fulfilled the inclusion and exclusion criteria underwent full-text review. For every selected full text, we extracted the following data if available: patients demographics, types of antimuscarinics used, placebo, dose, follow-up period, and Mini-Mental State Examination (MMSE) total score.* ***Results:*** *a total of 8*

studies from an initial 146 publications were selected. There were 8 antimuscarinic agents evaluated in the studies, including Oxybutynin, Darifenacin, Tolterodine, Trospium, Imidafenacin, Propiverine hydrochloride, Fesoterodine, and Solifenacin. Oxybutynin was shown to have largest effect towards the decline of MMSE score [Mean difference: -2.90; 95% CI: -4.07, -1.73]. Darifenacin and Tolterodine were also shown to be significant in the decline of total MMSE score, although still inferior to Oxybutynin. ***Conclusion:*** *the use of most antimuscarinics medication has little to no effect towards the cognitive function in the management of overactive bladder in elderly patients. However, Oxybutynin, Darifenacin, and Tolterodine was shown to have significant decrease in cognitive functions, as shown in the decline of total MMSE score.*

Keywords: *antimuscarinic drugs, cognitive functions, overactive bladder, mini-mental state examination (MMSE).*

INTRODUCTION

Overactive bladder (OAB) affects 17-41% of community-dwelling older adults.[1] It is best described as a chronic condition which is usually characterized with frequency and nocturia symptoms and urgency, with or without urge incontinence.[2,3] The prevalence of OAB is positively correlated with aging.[4] Not only does OAB cause urinary complaints, OAB may also cause falls and fractures in older adults.[4] The efficacy and tolerability of antimuscarinic therapy for the management of OAB is well established. For several years, antimuscarinics have been validated as the first-line medical treatment for OAB.[5]

Antimuscarinics therapy have several adverse effects, such as constipation, dry mouth, and blurred vision which happen due to the acetylcholine receptors inhibition. The CNS side effects include memory loss, insomnia, anxiety, headache, pain, and cognitive dysfunction.[5] The cholinergic system has an important role in cognitive functions and memory.

Elderly with Alzheimer's disease is more prone to get CNS side effects after taking antimuscarinics drugs. This tendency may also be caused by the blood-brain barrier (BBB) impairment.[6] In daily clinical setting, the antimuscarinic medication is only administered when the benefits outweigh the risks. The prescription of antimuscarinic drugs for geriatric population is often challenging due to the consideration regarding efficacy and side effects.[7] The available products of antimuscarinics include oxybutynin, solifenacin, tolterodine, darifenacin, propiverine hydrochloride, imidafenacin, fesoterodine, and trospium.[8]

The investigation about the effect of this drug on cognitive function in elderly remains scarce. Studies which investigate the effect of antimuscarinics on cognitive function in OAB patients are lacking. Consequently, the current available scientific evidence is not in accordance with clinical pictures. It is due to several reasons, such as the pre-existing cognitive impairment in elderly, comorbidities, geriatric problems, and various cognitive measurement tools. The objective of this study is to investigate the effect of antimuscarinics therapy on cognitive functions in OAB geriatric patients.

METHODS

Eligibility Criteria

This systematic review and meta-analysis aims to investigate the effect of antimuscarinic drug on cognitive functions in the management of overactive bladder in elderly. Our PICO is mentioned in **Table 1**. Searching strategy was not limited by date of publication and only full-text articles were used. The data searching process was not limited by language.

Information Sources

Studies were collected using several databases; namely PubMed, Science Direct, Cochrane, and EBSCOhost and obtained

Table 1. PICO

Patients	Elderly patients with overactive bladder (OAB)
Interventions	Antimuscarinic drugs
Comparisons	Placebo
Outcome	Cognitive functions

unpublished data through manual searching. The exact keywords used were: (antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*).

All keywords used were searched for their respective MeSH thesaurus. Data searching process was not limited by date of publication and only full-text articles were used. Article selection was not limited by English language. Article selection was done according to the search strategy recommended by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). Only studies investigating the effect of antimuscarinics on cognitive functions in elderly OAB patients were assessed for further analysis. Studies conducted in other than human and non-placebo controlled were excluded from the review. Data from all selected articles were extracted independently by three reviewers. Any disagreements were solved by consensus. Relevant parameters explored using Review Manager V5.3.

Study Selection and Data Extraction

All studies were screened for duplication. Duplication-free article underwent title and abstract examination based on predetermined inclusion and exclusion criteria. Selection of studies was done by three reviewers (ER, HE, and FW). In case of disagreement, resolution was achieved through discussion or a third party's adjudication. Studies which fulfilled the inclusion and exclusion criteria underwent full-text review. We extracted the following data from selected full text if available: patients demographics, types of antimuscarinics used (oxybutynin, darifenacin, tolterodine, trospium, imidafenacin, propiverine hydrochloride, fesoterodine, and solifenacin), placebo, dose, follow-up period, and Mini-Mental State Examination (MMSE) total score.

Criteria for Studies

Types of studies. This review included all studies that investigate the effect of antimuscarinic drug on cognitive functions in the management of overactive bladder in elderly. Types of literature included in this study were either clinical trial or cohort design. There were no date nor language restrictions of studies.

Types of outcome measures. The outcome measure of this study is the total score of MMSE which comprises of 5 parameters, namely orientation, registration, attention and calculation, recall, and language.

Data Collection and analysis. Data collected were relevant information about intervention,

Table 2. Database, search terms and number of articles retrieved.

Database	Search strategy	Hits
PubMed	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	20
Cochrane	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	9
ScienceDirect	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	113
EBSCOhost	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	4

characteristics and outcomes suits inclusion criteria formed by reviewers. Data analyses were conducted by two independent reviewers. Studies were appraised based on the Oxford Center of Evidence-Based Medicine Worksheet for therapy and analyzed using Review Manager 5.3 to study meta-analysis. Weighted mean differences (WMD) and odds ratio were used to analyze each study variables. The confidence interval was 95%, and p-value less than 0.05 are considered insignificant.

Cochrane Q test was used to study the heterogeneity of studies. Heterogeneity was assessed using I2 statistic. The I2 value less than 50% indicated that studies were homogeneous, consequently fixed effect model was used. The I2 value more than 50% indicated that studies were heterogeneous, and random effect model were used.

RESULTS

Literature Search

A total of 146 publications were initially retrieved (**Figure 1**). Of these, 106 studies were excluded due to duplication. Moreover, 28 were excluded during title and abstract screening. Eight studies underwent full-text appraisal, both qualitative and quantitative analysis.

Eight studies were assessed to estimate the effect of various antimuscarinic agents on the cognitive functions in the elderly OAB patients. There were 8 antimuscarinic agents evaluated in the studies. Oxybutynin was shown to have largest effect towards the decline of MMSE score [Mean difference: -2.90; 95% CI: -4.07, -1.73]. Darifenacin and Tolterodine were also shown to be significant in the decline of total MMSE score. However, the total MMSE score decline

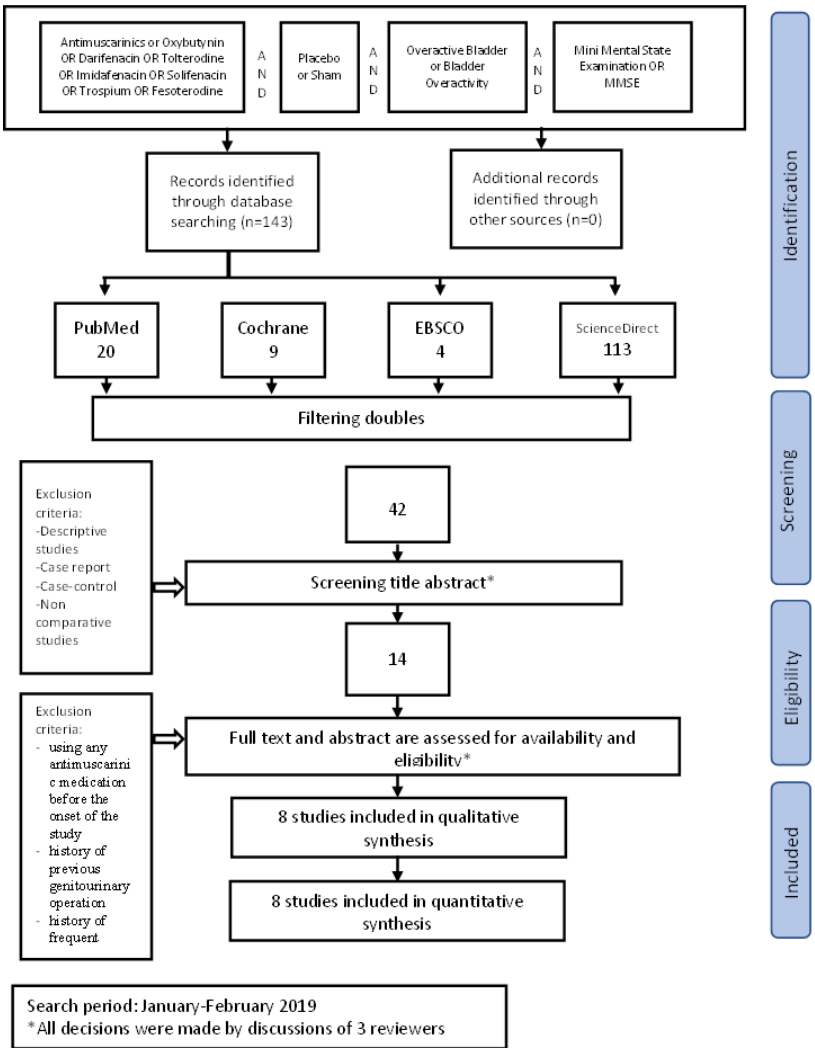

Figure 1. Study flow diagram.

mean difference of Darifenacin and Tolterodine was inferior compared to Oxybutynin. The total MMSE score decline mean difference of MMSE score in Darifenacin group was -2.70 (-4.03, -1.37), while in Tolterodine group was -1.60 (-3.04, -0.16). Other agents such as Trospium, Imidafenacin, Fesoterodine, and Solifenacin were not shown to decrease MMSE total score in elderly OAB patients. There was one study assessing the effect of Propiverine hydrochloride

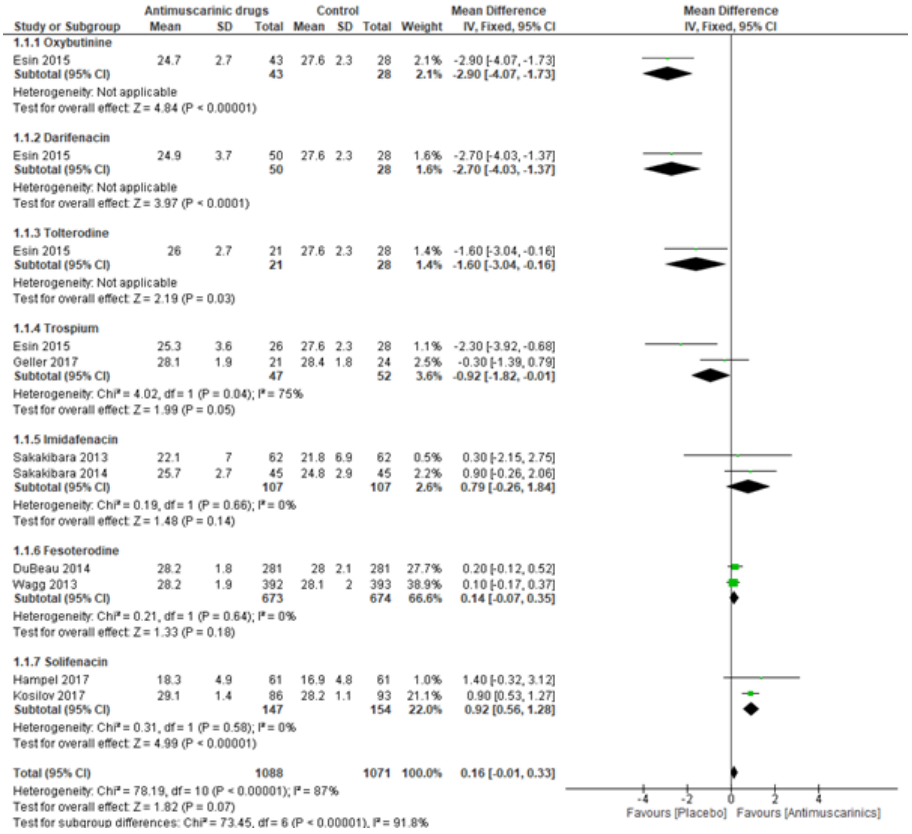

Figure 2.

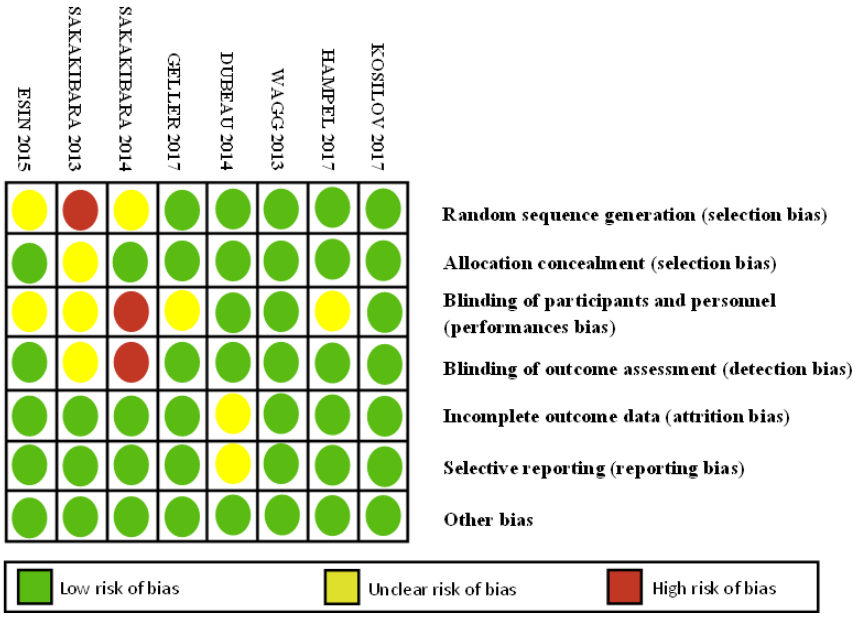

Figure 3. Risk of bias assessment of the included studies.

towards cognitive function, but the subject criteria was not elderly.

The risk of biases, as assessed by using version 2 of Cochrane risk-of-bias tool, can be seen on **Figure 3**. High risk of bias were found in Sakikabara 2013 and 2014. There was selection bias found in study by Sakakibara et al.[9] caused by the temporal availability of NIRS. In, Sakakibara et al.[10], there were no placebo control group nor blinding.

DISCUSSION

In the upcoming decades, the elderly population will increase. There will be a shift in the age composition of the older population.

The prevalence of OAB increases with aging. Studies revealed that OAB and detrusor overactivity may occur due to increased release of acetylcholine from nonneuronal and neuronal sources during bladder filling.[5] Antimuscarinics can inhibit this afferent activity. Moreover, the pathway may be altered in the urothelium of aged bladder because of increased purinergic receptor sensitivity and raised P2X3 receptor expression.[5] The other contributing factors to bladder dysfunction in the elderly include chronic ischemia and inflammation.

In geriatric population, OAB is debilitating, frequent, and troublesome situation. Based on the data delivered by American Diabetes Association and the National Kidney Foundation, it is revealed that one of two women and one of four men who visited outpatient geriatric clinic were present with OAB symptoms. In addition, dementia is also common in geriatric population with OAB. The prevalence of dementia increases as advancing age. Moreover, this condition is commonly associated with other geriatric syndromes.[8]

In addition, advancing age contributes to both OAB and cognitive impairment condition. Therefore, the proportion of elderly who harbors both conditions will consequently increase.

The diagnosis and management of OAB in elderly are affected by neurologic, cardiovascular disorders, musculoskeletal conditions, diabetes, and psychiatric disorders.[9] The patients are commonly prescribed multiple medications which can contribute to OAB symptoms. The medications taken can also interact with OAB drug treatment. Polypharmacy is defined as a condition when the patient is taking five or more drugs regularly. Besides, there are several factors which play an important role in the OAB management, including mobility disorders, cognitive impairment, bowel habits, and fluid intake.[10]

Esin et al[8] investigated the effect of antimuscarinic medications on elderly cognitive functions. It was shown that no cognitive impairment was observed in the patients involved in the study who were using these medications.[8] No cognitive impairment was observed in study population who had dementia at the beginning of the study. From the antimuscarinic medications being used in the study, oxybutinin and darifenacin group was shown to significantly decrease MMSE scores.

CNS adverse effects such as cognitive impairment might occur because many antimuscarinics can cross the blood-brain barrier. This issue is addressed as a serious consideration in antimuscarinic therapy for elderly OAB patients. The guidelines often recommended oxybutynin.[5] However, a high incidence of cognitive impairment is noted with the administration of this drug. Therefore, administration of oxybutynin is not recommended in frail elderly OAB patients.[8]

Oxybutynin is highly lipophilic compound, which allows it to cross the blood-brain barrier and causes effects on central nervous system (CNS). The high lipophilicity, neutrality, and small molecular size of oxybutynin may allow the drug to cross the blood-brain barrier and skin more easily relative to other antimuscarinic agents.[12]

Oxybutynin chloride is the longest commercially available and approved antimuscarinic drug for the treatment of OAB. To date, there is no study consistently demonstrated that oxybutynin chloride has superior efficacy compared to other medications within this drug class.[13] However, it has been shown that Oxybutynin has the worst adverse effect profile. Several studies suggest that Oxybutynin (either immediate [IR] or extended release [ER]) has a significantly negative effect on cognitive

function.[13] Kay et al reported that a 3-week treatment with Oxybutynin ER resulted in significant memory impairment which was shown on delayed recall performance in the Name-Face Association test. Even in young patients, it has been reported that the use of Oxybutynin resulted in hallucinations and episodes of psychosis.[14] This systematic review and meta-analysis shows similar result as the previous studies. Oxybutynin was shown to have the worst adverse effect profile towards the decline in the MMSE score. The mean difference of MMSE score between Oxybutynin group and control group was -2.90 (-4.07, -1.73; 95% CI).

Darifenacin was previously shown to have minimal CNS penetration. In an autoradiographic study in rats by Devineni et al.[15], it is reported that levels of C-darifenacin in the brain following a single intravenous injection remain low. Darifenacin is a substrate for the P-glycoprotein-mediated efflux transporter. This property is not reported for other antimuscarinic agents. Therefore, darifenacin which crossed the blood-brain barrier and entering the CNS can be actively removed. This system may reduce the potential CNS adverse effects. CNS concentrations of darifenacin are considered low, indicated by its lipophilicity, molecular size, and positive molecular charge.[16] On the contrary, this systematic review and meta-analysis showed that Darifenacin had a significant adverse effect towards the decline of MMSE score. In a study conducted by Esin et al, it was shown that Darifenacin may decline the MMSE score by -2.70 (-4,03, -1,37; 95% CI) points. The difference may result from the decreased blood-brain barrier P-glycoprotein in elderly. In a study conducted by Assema et al which acquired sixty minutes dynamic (R)-[11C]verapamil scans with metabolite-corrected arterial plasma input curves, it was shown that The volume of distribution of (R)-[11C]verapamil increases with age in several cortical brain regions, strongly suggesting a progressive decrease in BBB Pgp function with age.[17]

In a study conducted by Nilvebrant et al, it is previously reported that tolterodine has low lipophilicity and low CNS penetration. The brain/blood ratio for tolterodine is 0.1 to 0.3 for radioactivity in mice.[18-19] Despite its low lipophilicity, this current study showed that Tolterodine still had a negative adverse effect towards the decline of MMSE score. Esin et al showed that Tolterodine group had -1.60 (-3.04,-0.16; 95% CI) points less than control group. The decline was considered clinically insignificant.

Fesoterodine is one of the antimuscarinic agents which shows minimal CNS adverse effects. It has been investigated that the lipophilicity of 5-hydroxymethyl tolterodine, was 10 times less lipophilic than those for tolterodine, solifenacin, or oxybutynin. Therefore, fesoterodine had least propensity of CNS effects.[20-21] The result of this study showed that Fesoterodine had no effect towards MMSE score between intervention group and control group which is in line with its pharmacological profile.

Solifenacin was shown to have a favorable outcome towards MMSE score in Elderly. Two previous studies showed a higher MMSE score in Solifenacin group compared to placebo. Compared to other muscarinic agents, Solifenacin was shown to have the best safety profile on cognitive impairment in elderly. The MMSE score in Solifenacin group was 0.92 (0.56, 1.28; 95% CI) points higher than placebo.

Sakakibara et al.[9] investigated the role of Imidafenacin on bladder and cognitive function in neurologic OAB patients.[9] The study included sixty-two subjects (25 men, 37 women, mean age 70 years with OAB due to neurologic diseases) which mostly had mild cognitive decline (mean MMSE 21.8). It was shown that Imidafenacin significantly ameliorated urinary urgency, nighttime urinary frequency, and quality of life index ($p < 0.05$) without cognitive worsening, with a trend of prefrontal activation. Three cognitive measures (MMSE, FAB, ADAS-cog) did not change significantly in a 3-months period.[9]

In 2014, Sakakibara et al.[10] investigated the effect of Imidafenacin on cognitive safety and overall tolerability in clinical use. The patients enrolled in the study were assessed for their total MMSE score at baseline, 24-, and 48- weeks after treatment. There were 187 patients enrolled in the study. There was no significant decrease noted in the MMSE scores in the patients during follow up. Furthermore, the absence of

evidence suggesting any safety issues in the study provide confirmation that Imidafenacin can be used safely for cognitively vulnerable patients with OAB.10 In this study, the use of Imidafenacin was shown to have a favorable outcome. Compared to placebo, MMSE score in Imidafenacin group was higher by 0.79 (-0.26, 1.84, 95% CI) points.

CONCLUSION

The use of most but not all antimuscarinics medication has little to no effect on the cognitive function in the management of overactive bladder in elderly patients. However, Oxybutynin, Darifenacin, and Tolterodine was shown to have significant decrease in cognitive functions, as shown in the decline of total MMSE score.

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REFERENCES

1. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20:327-36.
2. Haylen BT, Freeman RM, Swift SE, et al. International Urogynecological Association; International Continence Society; Joint IUGA/ICS Working Group on Complications Terminology. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. Neurourol Urodyn. 2011;308:2e12.
3. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U. Standardisation sub-committee of the International Continence Society. The standardization of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourology and Urodynamics. 2002;21:167-78.
4. Brown JS, Vittinghoff E, Wyman JF, Stone KL, Nevitt MC, Ensrud KE, Grady D. Urinary incontinence: Does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatrics Soc. 2000;48:721-5.
5. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. Eur Urol. 2008; 54:543-62.
6. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: A review of progress. J Neurol Neurosurg Psychiatry. 1999;66:137-47.
7. Feinberg M. The problems of anticholinergic adverse effects in older patients. Drugs & Aging. 1993;3:335-48.
8. Esin E, Ergen A, Cankurtaran M, et al. Influence of antimuscarinic therapy on cognitive functions and quality of life in geriatric patients treated for overactive bladder. Aging & Mental Health. 2015;19(3):217-23. DOI: 10.1080/13607863.2014.922528.
9. Sakakibara R, Tateno F, Yano M, et al. Imidafenacin on bladder and cognitive function in neurologic OAB patients. Clin Auton Res. 2013;23:189–95. DOI 10.1007/s10286-013-0200-3.
10. Sakakibara R, Hamano H, Yagi H. Cognitive safety and overall tolerability of imidafenacin in clinical use: a long-term, open-label, post-marketing surveillance study. LUTS. 2014;6:138–144. DOI: 10.1111/luts.12068.
11. Scheife R, Takeda M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. Clin Ther. 2005;27:144–53.
12. Anderson RU, Mobley BB, Saltzstein D, et al. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. J Urol. 1999;161:1809–12.
13. Katz IR, Sands LP, Bilker W, DiFilippo S, Boyce A, D'Angelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc. 1998;46(1):8–13.
14. Kay G, Crook T, Rekeda L, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. Eur Urol. 2006;50(2):317–26.
15. Devineni D, Skerjanec A, Woodworth TG. Low central nervous system (CNS) penetration by darifenacin, a muscarinic M3 selective receptor antagonist, in rats. Proc Br Pharmacol Soc Summer 2005 (abstr092P) http://www.pa2online.org/abstracts/Vol3Issue2abst092P.pdf.
16. Skerjanec A, Devineni D. Affinity of darifenacin for the p-glycoprotein efflux pump: a mechanism contributing to the CNS sparing profile? Abstract presented at British Pharmacological Society Winter Meeting, 14-16 December, 2004, Newcastle, UK.
17. van Assema DM, Lubberink M, Boellaard R, et al. P-glycoprotein function at the blood-brain barrier: effects of age and gender. Mol Imaging Biol. 2012;14(6):771–6. doi:10.1007/s11307-012-0556-0.
18. Nilvebrant L. The mechanism of action of tolterodine. Rev Contemp Pharmacother. 2000;11:13-27.

19. Malhotra B. Lipophilicity of 5 Hydroxymethyl Tolterodine, the active metabolite of Fesoterodine. Uro Today Int J. 2008;1(15). DOI: 10.3834/uij.1939-4810.2008.06.35.
20. DuBeau CE, Kraus SR, Griebling TL, et al. Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo-controlled trial. J Urol. 2014;191:395-404. DOI: 10.1016/j.juro.2013.08.027.
21. Wagg A, Khullar V, Marschall-Kehrel D, Michel MC, Oelke M, Darekar A. Flexible-dose Fesoterodine in elderly adults with overactive bladder: Results of the randomized, double-blind, placebo-controlled study of Fesoterodine in an aging population trial. JAGS. 2013; 61:185–93. DOI: 10.1111/jgs.12088.
22. Lee YS, Lee KS, Kim JC, et al. Persistence with solifenacin add-on therapy in men with benign prostate obstruction and residual symptoms of overactive bladder after tamsulosin monotherapy. Int J Clin Pract. 2014;68(12):1496-502. doi: 10.1111/ijcp.12483. Epub 2014 Oct 6.
23. Geller EJ, Dumond JB, Bowling JM, et al. Effect of trospium chloride on cognitive function in women aged 50 and older: a randomized trial. Female Pelvic Med Reconstr Surg. 2017;23: 118–23. DOI: 10.1097/SPV.0000000000000374.
24. Hampel C, Betz D, Burger M, Nowak C, Vogel M. Solifenacin in the elderly: Results of an observational study measuring efficacy, tolerability, and cognitive effects. Urol Int. DOI: 10.1159/000455257.
25. Kirill Kosilov, Irina Kuzina, Vladimir Kuznetsov, et al. Cognitive functions and health-related quality of life in men with benign prostatic hyperplasia and symptoms of overactive bladder when treated with a combination of tamsulosin and solifenacin in a higher dosage. Aging Male. 2017. DOI: 10.1080/13685538.2017.1398723.
26. Ouslander JG. Geriatric considerations in the diagnosis and management of overactive bladder. Urology. 2002; 60 (5):Supp 1. DOI: 10.1016/S0090-4295(02)01795-8.

The Effect of Hyperfiltration on Kidney Function in Living Donor Kidney Transplantation: A Prospective Cohort Study

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ABSTRAK

Latar belakang: *donasi ginjal dengan donor hidup merupakan prosedur medis yang aman. Kualitas hidup donor merupakan luaran utama dan dicapai melalui hiperfiltrasi ginjal yaitu mekanisme kompensasi untuk mempertahankan fungsi ginjal setelah nefrektomi unilateral. Penelitian mengenai hiperfiltrasi ginjal pada donor hidup masih terbatas. Penelitian ini bertujuan untuk menjelaskan mekanisme hiperfiltrasi ginjal termasuk dampaknya terhadap fungsi ginjal dalam 30 hari setelah nefrektomi, serta mengevaluasi keamanan donasi ginjal.* ***Metode:*** *desain penelitian ini adalah kohort prospektif yang diikuti oleh 46 orang donor hidup pada April hingga Desember 2019. Fungsi ginjal 30 hari setelah nefrektomi dievaluasi melalui estimasi laju filtrasi glomerulus (LFG) dan rasio albumin-kreatinin. Subjek penelitian dikelompokkan berdasarkan luaran pada hari ke-30, menjadi kelompok adaptif (LFG > 60 mL/menit/1,73 m^2) dan maladaptif (LFG < 60 mL/menit/1,73 m^2). Pemeriksaan resistive index (RI) ginjal, vascular endothelial growth factor (VEGF), neutrophil gelatinase-associated lipocalin (NGAL) dan heparan sulfat (HS) dilakukan secara serial sejak sebelum nefrektomi hingga 30 hari setelahnya. Luaran dianalisis dengan analisis multivariat.* ***Hasil:*** *empat puluh orang donor dianalisis hingga akhir, sebagian besar merupakan perempuan (67,5%). Rerata usia dan indeks massa tubuh (IMT) subjek berturut-turut adalah 45,85 (SB 9,74) tahun dan 24,36 (SB 3,73) kg/m^2. Sembilan belas donor (47,5%) mengalami hiperfiltrasi maladaptif. Proses hiperfiltrasi ditunjukkan oleh perubahan bermakna pada RI arteri ginjal serta kadar VEGF, NGAL dan HS urin (p<0,005). Tidak ada perbedaan bermakna masing-masing parameter antara kelompok adaptif dan maladaptif. Faktor perancu (IMT > 25 kg/m^2, hubungan donor-resipien, usia > 40 tahun dan kekakuan arteri) secara bermakna memengaruhi hiperfiltrasi ginjal (p<0,05).* ***Kesimpulan:*** *proses hiperfiltrasi tidak memengaruhi fungsi ginjal donor 30 hari pascanefrektomi. Berbagai faktor lain dapat memengaruhi proses hiperfiltrasi dan fungsi ginjal. Penelitian lebih lanjut diperlukan untuk mengevaluasi fungsi ginjal dalam jangka waktu yang lebih panjang.*

Kata kunci: *donor Hidup, heparan sulfat, hiperfiltrasi, neutrophil gelatinase-associated lipocalin, resistive index, transplantasi ginjal, vascular endothelial growth factor.*

ABSTRACT

Background: *living kidney donation is a safe medical procedure. Kidney function after donation is crucial for donors' health and quality of life. Kidney hyperfiltration is a compensatory mechanism, which will preserve kidney function after unilateral nephrectomy. The number of studies regarding hyperfiltration in living kidney donors is limited. Our study aimed to explain kidney hyperfiltration mechanism and evaluate its effect on the kidney function within 30 days after surgery.* ***Methods:*** *our study was a prospective cohort study with 46 living-kidney donors participating in the study between April and December 2019. We evaluated main outcomes, the 30-day post-surgery kidney function, which was evaluated by calculating estimated glomerular filtration rate (eGFR) and Urinary Albumin to Creatinine Ratio (ACR). The subjects were categorized into two groups based on their 30-day outcomes, which were the adaptive (eGFR > 60 mL/min/1.73 m^2 and/or ACR > 30 mg/g) and maladaptive (eGFR < 60 mL/min/1.73 m^2 and/or ACR > 30 mg/g) groups. A series of evaluation including calculating the renal arterial resistive index (RI) and measuring urinary vascular endothelial growth factor (VEGF), neutrophil gelatinase-associated lipocalin (NGAL), and heparan sulfate (HS) levels were performed before surgery and serially until 30 days after surgery. Multivariate analysis with adjustments for confounding factors was done.* ***Results:*** *forty donors were included and mostly were female (67.5%). The average age and body mass index (BMI) were 45.85 (SD 9.74) years old and 24.36 (SD 3.73) kg/m^2, respectively. Nineteen donors (47.5%) had maladaptive hyperfiltration outcomes. The hyperfiltration process was demonstrated by significant changes in renal arterial RI, urinary VEGF, NGAL, and HS levels ($p<0.005$). There was no significant difference regarding RI, urinary VEGF, NGAL, and HS levels between both groups. Several confounding factors (BMI over 25 kg/m^2, familial relationship, age over 40 years old, and arterial stiffness) were significantly influenced by kidney hyperfiltration and outcomes ($p<0.05$).* ***Conclusion:*** *the hyperfiltration process does not affect the 30-day post-nephrectomy kidney function of the donors. Several other factors may influence the hyperfiltration process and kidney function. Further study is necessary to evaluate kidney function and its other related variables with a longer period of time study duration.*

Keywords: *heparan sulfate, hyperfiltration, living-donor, neutrophil gelatinase-associated lipocalin, resistive index, kidney transplantation, vascular endothelial growth factor.*

INTRODUCTION

Kidney transplantation is an ideal treatment of choice for patients with end-stage renal disease (ESRD). Compared to lifetime dialysis, kidney transplant is associated with lower mortality and better quality of life.[1] Living kidney donation is considered to be a relatively safe procedure that does not harm donors in the long-term.[2-4] A compensating mechanism attempted by the remaining kidney is called hyperfiltration.[5] It occurs post-nephrectomy and will increase renal blood flow. Such mechanism is expected to preserve donor's kidney function.[6] However, the mechanism is not always successful. A failed hyperfiltration process is known as maladaptive hyperfiltration.[7] A study conducted by Choi[6] and Kwon.[8] reported that there were 40.38% and 55.8% donors, respectively, who developed chronic kidney disease (CKD) in 6 months period after kidney donation procedure. Unfortunately, none of these studies investigated the factors that affect the decreasing kidney function.

Adaptive and maladaptive hyperfiltration mechanisms are associated with renal blood flow and glomerular hypertrophy.[9,10] Renal blood flow is evaluated by using resistive index (RI)[11]; while glomerular hypertrophy is characterized by an increase in vascular endothelial growth factor (VEGF) level. VEGF is an important mediator in angiogenesis and a survival factor to maintain endothelial cells.[12] Nevertheless, it is still unclear whether changes in these parameters can significantly affect adaptive and maladaptive hyperfiltration. Schrijvers et al.[13] have reported that VEGF is related to glomerular and peritubular endothelial cells proliferation post-nephrectomy in animal models. To date, no study has been conducted on human urinary VEGF level in relation to post-uninephrectomy kidney hyperfiltration and its effects on adaptive and maladaptive hyperfiltration.

Renal function has also been associated with other factors related to nephrectomy including ischemic reperfusion injury and renal

cell hypoxia. Both of these conditions promote increased renal ischemic biomarkers levels such as neutrophil gelatinase-associated lipocalin (NGAL) and heparan sulfate proteoglycan.[14-16] These two biomarkers are also necessary to be tested in our study since changes in their levels can alter VEGF level.

Our study aimed to determine the incidence of maladaptive hyperfiltration in kidney donors within 30 days after nephrectomy. The study also aimed to compare RI, urinary VEGF, urinary NGAL, and urinary heparan sulfate proteoglycan levels between donors with adaptive and maladaptive hyperfiltration. Moreover, our research may provide basic profile of Indonesian living kidney donor transplantation that can be further utilized to develop kidney transplantation programs in Indonesia.

METHODS

Our study was a prospective cohort study, which was based on prognostic research program. The study was conducted at Cipto Mangunkusumo Hospital in Jakarta between November 2018 and February 2020. The inclusion criteria were living kidney donor patients aged older than 18 years old, who had agreed to participate in the study and had signed informed consent form; while the exclusion criteria were consistent with the National Consensus of Indonesian Society of Nephrology (InaSN) consist of functional or structural abnormality of kidney, uncontrolled hypertension, chronic diseases, alcohol and drugs abuse, viral infections, malignancy, pregnancy, psychosis or mental retardation, severe neurological deficiency or impairment, and other rare and or severe health condition. Total sampling method was used.

This study has been approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia on March 25th, 2019 (reference number KET-292/UN2.F1/ETIK/PPM.00.02/2019).

Serial examinations of calculating RI and measuring urinary VEGF, urinary heparan sulfate proteoglycan levels as well as performing routine blood test and urinalysis were carried out before nephrectomy and on day 1, 2, 3, 7 and 30 after nephrectomy. Urinary NGAL level was measured before and within 6 hours after nephrectomy. Renal resistive index (RI) was assessed using doppler ultrasonography (USG). Four main arteries were evaluated in our study, i.e. the renal artery, segmental artery, interlobar artery, and arcuate artery. Pulse wave velocity (PWV) measured using SphygmoCor® at the same time with initial measurement of blood pressure, height and weight. Samples for routine blood tests were obtained by phlebotomy; while samples for routine urinalysis were taken using mid-stream technique. Modification of diet in renal disease (MDRD) formula was used to determine donors' estimated glomerular filtration rate (eGFR). Measurement for urine biomarkers (VEGF, NGAL and heparan sulfate [HS]) levels were done using ELISA method with R&D Quantikine ELISA kit (Minnesota, USA) for urinary VEGF and NGAL, Cusabio ELISA kit (Wuhan, China) for urinary HS level. Subjects were then categorized into two groups, which were the adaptive group (subjects with eGFR >60 mL/min/1.73 m^2 and ACR <30 mg/g on day 30) and maladaptive group (subjects with eGFR <60 ml/min/1.73 m^2 and ACR >30 mg/g on day 30).

Shapiro Wilk test was used to determine data distribution. Numerical data were presented in average with standard deviation or median with minimum and maximum range. Categorical data were presented in frequency and percentage. Changes of RI, urinary VEGF, NGAL, heparan sulfate and also eGFR and ACR within both groups before and after nephrectomy were compared using paired T test for data with normal distribution and Wilcoxon test for non-normally distributed data. Values of each parameters between the two groups were compared using independent T test or Mann Whitney test. Subgroup analysis was performed to evaluate possible confounding factors including age of >40 years, BMI >25 kg/m^2, biological relationship to recipients and PWV of >8.33 m/s (50^{th} percentile). All statistical analyses were processed using SPSS software program version 20.0. Interim analysis was performed after six months of data collection. 25 subjects were included.

RESULTS

Forty-six living kidney donors were included. During the study, one patient refused to enroll

in the study and five patients were excluded due to lost to follow-up. Forty subjects, who were mostly female (27 donors, 67.5%), were included in the final analysis with average age of 45.85 years. Most donors were not biologically related to their recipients (55%). (**Table 1)**

Table 1. Donors' demographic, clinical and laboratory characteristics

Characteristics	Value (N=40)
Donor-recipient relationship, n (%)	
- Related	18 (45)
- Unrelated	22 (55)
Sex, n (%)	
- Male	13 (32.5)
- Female	27 (67.5)
Age (years), mean (SD)	45.85 (9.74)
Age group, n (%)	
- < 30 years old	1 (2.5)
- 30 – 39 years old	11 (27.5)
- 40 – 49 years old	14 (35)
- 50 – 59 years old	10 (25)
- > 60 years old	4 (10)
BMI (kg/m^2), mean (SD)	24.36 (3.73)
BMI group, n (%)	
- Underweight (<18.5)	1 (2.5)
- Normal (18.5 – 22.9)	16 (40)
- Overweight (23.0 – 24.9)	5 (12.5)
- Obese I (25.0 – 29.9)	14 (35)
- Obese II (> 30)	4 (10)
Systolic blood pressure (mmHg), median (min-max)	120 (90 - 145)
Diastolic blood pressure (mmHg), median (min-max)	80 (60 - 90)
Pulse wave velocity, (m/s), mean (SD)	8.52 (1.14)

Nineteen subjects (47.5%) were found to have maladaptive kidney function within 30 days after nephrectomy. GFR of both groups were more likely to decrease in day 1 and day 2 before rising on day 3 onwards. However, in subjects of maladaptive group, the increase in GFR was not at the same pace, which then resulted in failure of kidney function. There was a significant difference of GFR between adaptive and maladaptive groups (57.00 mL/min/1.73 m^2 vs. 70.10 mL/min/1.73 m^2; p< 0.001). In contrast, the ACR was not significantly different between both groups (18.46 vs. 10.10; p 0.055) (**Table 2**).

The cut-off value for GFR before the subjects underwent nephrectomy between adaptive and maladaptive group was 104.60 (76.2% sensitivity, 72.3% specificity) with Area Under Curve of 85.7% (CI 95% 74.3 – 97.1).

Despite several insignificant results of RI, there was a consistent trend found in renal, segmental, interlobar and arcuate arteries. (**Figure 1**)

The RI increased on day 2 following the nephrectomy before decreasing on day 7 and day 30. **Figure 2** shows significant RI difference of arcuate arteries between day 2 and day 30, which was found only in the adaptive group.

Our study found no significant difference regarding RI between adaptive and maladaptive groups as shown in **Table 3**.

Several results of factors affecting hyperfiltration mechanism are presented in

Tabel 2. Changes in eGFR and ACR between maladaptive and adaptive groups

Variables	Day	Maladaptive (n=19)	Adaptive (n=21)	p
eGFR (mL/min/1.73 m^2)	Dpreop, mean (SD)	92.94 (13.21)	111.17 (11.38)	<0.001
	D1, mean (SD)	64.06 (14.54)	80.20 (17.27)	0.003
	D2, median (min-max)	51.70 (27.10–74.80)	62.10 (49.70–131.00)	0.002
	D3, median (min-max)	55.80 (30.10–74.80)	64.30 (51.00–104.90)	<0.001*
	D7, mean (SD)	54.17 (9.37)	74.55 (15.23)	<0.001
	D30, median (min-max)	57.00 (41.10–71.10)	70.10 (60.10–119.10)	<0.001*
ACR	Dpreop, median (min-max)	16.50 (1.50–218.30)	9.10 (1.20–38.20)	0.062*
	D1, median (min-max)	72.05 (17.80–661.60)	49.10 (9.80–96.70)	0.114*
	D2, median (min-max)	58.90 (10.22–174.00)	39.70 (13.40–109.40)	0.020*
	D3, median (min-max)	41.95 (10.22–268.30)	38.10 (4.00–125.00)	0.465*
	D7, median (min-max)	31.90 (3.70–265.10)	12.50 (3.60–96.80)	0.186*
	D30, median (min-max)	18.46 (3.50–555.60)	10.10 (3.00–25.60)	0.055*

*Mann-Whitney Test

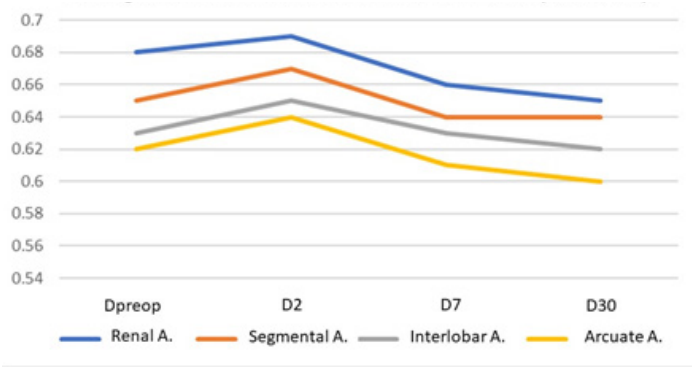

Figure 1. Changes in resistive index before and after nephrectomy.

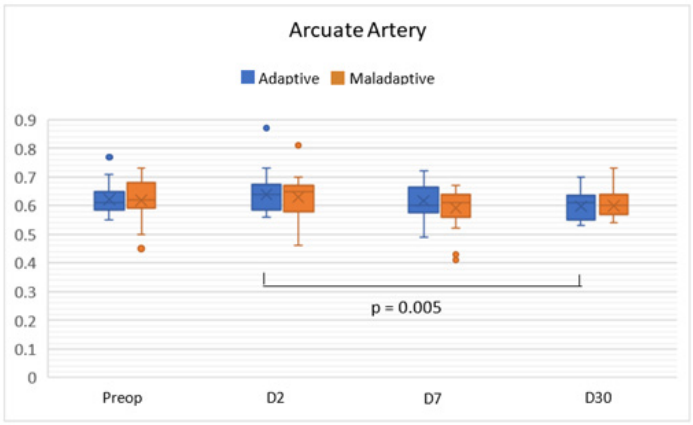

Figure 2. RI difference of arcuate arteries between day 2 and day 30.

Table 3. Changes in resistive index between adaptive and maladaptive groups

Resistive Index	Adaptive Hyperfiltration (n=20)	Maladaptive Hyperfiltration (n=19)	P
Pre-op, mean (SD)			
- A. Renal	0.68 (0.03)	0.68 (0.07)	0.91
- A. Segmental	0.65 (0.05)	0.65 (0.06)	0.89
- A. Interlobar	0.63 (0.05)	0.62 (0.06)	0.67
- A. Arcuate	0.62 (0.05)	0.62 (0.07)	0.89
D2			
- A. Renal	0.67 (0.63 – 0.80)	0.70 (0.06)	0.73*
- A. Segmental, mean (SD)	0.66 (0.06)	0.67 (0.07)	0.53
- A. Interlobar, mean (SD)	0.64 (0.06)	0.66 (0.07)	0.41
- A. Arcuate	0.64 (0.56 – 0.87)	0.63 (0.07)	0.65*
D7			
- A. Renal, mean (SD)	0.67 (0.06)	0.65 (0.05)	0.32
- A. Segmental, mean (SD)	0.64 (0.04)	0.63 (0.05)	0.46
- A. Interlobar, mean (SD)	0.64 (0.06)	0.62 (0.05)	0.37
- A. Arcuate	0.62 (0.06)	0.61 (0.41 – 0.67)	0.23*
D30			
- A. Renal, mean (SD)	0.66 (0.05)	0.65 (0.08)	0.45
- A. Segmental, mean (SD)	0.64 (0.04)	0.63 (0.07)	0.31
- A. Interlobar, mean (SD)	0.61 (0.06)	0.62 (0.07)	0.78
- A. Arcuate	0.60 (0.05)	0.60 (0.06)	0.88

*Mann-Whitney Test

Tabel 4. Changes in urinary VEGF, NGAL, and heparan sulfate levels in maladaptive and adaptive groups.

Biomarker	Adaptive (n = 21)	Maladaptive (n = 19)	p
VEGF (pg/mL), median (min-max)			
- Prenephrectomy	20.31 (8.67–112.20)	26.91 (9.54 – 298.60)	0.371
- D22	173.40 (20.98–670.15)	221.40 (30.84 – 970.86)	0.250
- D7	31.25 (9.05–299.35)	45.39 (7.85 – 414.55)	0.147
- D30	19.67 (4.76–1051.44)	62.50 (8.01 – 2244.5)	0.129
NGAL (ng/mL), median (min-max)			
- Prenephrectomy	4.5 (0.80–43.30)	4.9 (1.00–68.50)	0.809
- D1	9.40 (1.20–214.90)	11.20 (0.90–46.30)	0.450
Heparan Sulfat (ng/mL), median (min-max)			
- Prenephrectomy	13.30 (5.53 – 400.00)	11.52 (5.76 – 82.14)	0.461
- D2	12.148.84 (294.16 – 3.2745.52)	14.287.96 (1136.22 – 28.801.69)	0.425
- D7	193.94 (9.69 – 8.379.05)	122.66 (11.56 – 9.020.03)	0.857
- D30	33.71 (6.67 – 916.35)	58.45 (6.45 – 468.46)	0.881

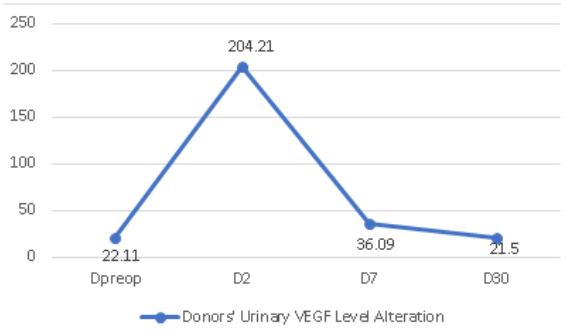

Figure 3. Changes in urinary VEGF levels before and after nephrectomy.

the following tables. A surge of urinary VEGF level on the second day after nephrectomy is demonstrated in **Figure 3**.

VEGF levels rose significantly on day 2 following the nephrectomy ($p<0.001$) before decreasing on day 7 and day 30 nearly to the baseline. Not with standing the statistically insignificant results (**Table 4**), urinary VEGF levels in maladaptive group were likely to be higher compared to those in the adaptive group.

Urinary NGAL and HS levels significantly increased after nephrectomy in both groups ($p<0.001$). Urinary NGAL level was insignificantly higher in maladaptive group. The median of urinary NGAL level before nephrectomy was 4.5 mg/mL and the level significantly rose ($p <0,001$) within four to six hours after nephrectomy (up to 11.00 mg/mL). The median urinary HS level was 12.41 ng/mL. Urinary heparan sulfate levels on day 2, 7 and 30 were found to be significantly higher compared to initial pre- nephrectomy level ($p<0,001$). Changes in urinary NGAL and HS levels. (**Table 4)**

Using a subgroup analysis method, there were four adjustments that had been made based on possible confounding factors (age, donor-recipient relationship, arterial stiffness and BMI). These factors were adjusted to the following parameters below in order to evaluate their correlations ($p<0.05$):

1. Renal artery resistive index before and after nephrectomy
2. Urinary VEGF level before and after nephrectomy
3. Urinary NGAL level before and after nephrectomy
4. Urinary HS level before and after nephrectomy
5. eGFR prior to surgery and after 30 days post nephrectomy
6. ACR prior to surgery and after 30 days post nephrectomy.

BMI >25 kg/m^2 is associated with lower VEGF level on day 7 post surgery. Age over 40 years old, Biological relation related to their recipients and higher PWV are several factors that give rise to lower kidney function. Higher PWV is related to renal artery RI on day 1 and day 7 post-nephrectomy.

DISCUSSION

Based on the donor's characteristics, the proportion of biologically-related donor is lower compared to unrelated donor (45% and 55%, respectively). Our findings differ from previous studies.[17,18] The average age of donors in our study was 45.85 years (SD 9.74). There were 13 donors (32.5%) aged over 50 years old. Older donor age is correlated to strict evaluation and comorbidities.[18]

Subjects in this study are dominated by female donors (67.5%). A study by Bloembergen, et al.[19] reported the same finding in which living kidney donors were dominated by female (RR 1,28, $p < 0.001$). Several underlying reasons that may affect one's decision in organ donations are socioeconomic status, various understanding levels of organ donation, family background and psychological ties, influences from family opinions, religion, culture, and belief in medical procedures for organ donation affect.[19]

The average BMI of our subjects was relatively high, i.e. 24.36 kg/m^2 (SD 3.73), which fell in the overweight category based on the Asia-Pacific WHO BMI classification.[20] Living donors with obesity tend to have higher risk of post surgery complications, longer inpatient recovery time, infection, hypertension and lower kidney function. Donors with BMI >35 kg/m^2 are not recommended to proceed undergoing transplantation procedure.[21]

Arterial stiffness was measured using PWV and it was concluded that average PWV in donors of our study was higher than normal population (7.2 m/s). Cited from Fesler et al.[22], we know that living kidney donors with higher PWV tend to show lower chance of successful adaptive hyperfiltration process after uninephrectomy.

Regarding changes in eGFR and ACR, at the end of our study, we found that there were significant difference between the two groups. Significant difference was only found in eGFR (57.00 mL/min/1.73 m^2 vs. 70.10 mL/min/1.73 m^2) with $p < 0.001$. On the other hand, ACR was not significantly different between both groups (18.46 vs. 10.10; $p = 0.055$). Our result is in line with results demonstrated by Yoon et al.[23] study.

The hyperfiltration mechanism was evaluated by calculating 30-day post-surgery eGFR and ACR. Donors who had eGFR < 60 mL/min/1.72 m^2 and/or ACR > 30 were categorized as having maladaptive hyperfiltration. Prior to nephrectomy, eGFR level in maladaptive group was significantly lower compared to the adaptive group. Therefore, initial kidney function is a key factor to determine success of hyperfiltration process. The cut-off point for initial kidney function in our study was 104.60 ml/min/1.73 m^2. Donors who initially had lower eGFR than the cut-off point would develop higher risk for having eGFR < 60 mL/min/1.73 m^2 within 30 days after nephrectomy. Such findings are in line with results of a study conducted by Kwon et al.[8] Moreover, Kwon et al mentioned that the results from 30 days after nephrectomy will predict long-term kidney function. Donors with low kidney function within a month after surgery tend to develop CKD.

The increase in RI on day 2 after nephrectomy, which was then followed by reduction on day 7 and day 30 after nephrectomy in our study, showed that there were changes in blood flow following the nephrectomy.[24] Increase of RI on day 2 after surgery was caused by increase of renal blood; while renal vascular resistance dominantly decreased in systolic compared to diastolic components.[25] This mechanism is caused by vascular relaxation triggered by nitric oxide (NO), a vasodilator which is increasing on day 2 after nephrectomy and decreasing after the first week.[26,27] There was no significant difference regarding RI between adaptive and maladaptive groups, which suggests that RI has no effect on kidney function within 30 days after nephrectomy. However, a significant difference of RI of arcuate artery between day 2 and day 30 in adaptive group suggests that prolonged increased of RI may be associated with lower kidney function.

Arcuate artery is the ideal location to evaluate alteration of RI in donors after nephrectomy. Anatomically, arcuate artery is closest to glomerulus; therefore, any disturbance in glomerulus will be reflected better in arcuate artery than in any other location.[28] However, there was a statistically insignificant trend of RI alteration in both groups, which then lead to a conclusion that RI does not affect kidney function within 30 days after nephrectomy.

The alteration of urinary VEGF level after nephrectomy is considered to be associated with ischemic injury and renal cells hypoxia, as well as hypertrophic response of renal cells. Ischemic-related surge of VEGF may take place within 1-2 hours; while hypertrophy-related surge of VEGF normally takes place during the first two days.[29-31]

Our study could not provide evidences that the increase of VEGF level was caused by ischemia. However, the increase was probably related to hypertrophic response of renal cells.[13,32] Moreover, there was no significant difference of urinary VEGF levels between adaptive and maladaptive group. The result suggests that urinary VEGF level as a marker of hyperfiltration does not affect kidney function within 30 days after nephrectomy.

The increase in urinary NGAL level after nephrectomy suggests that there is hyperfiltration-related acute kidney injury;[33] however, it has no association to kidney function within 30 days after nephrectomy. Heparan sulfate proteoglycan level, which increased on day 2 after nephrectomy, is associated with ischemia. However, as there were no significant differences between the adaptive and maladaptive groups, the surge was hypothesized to be a physiologic response and did not cause any decline in kidney function.

Using subgroup analysis to adjust the results based on several confounding factors, the donors who are over 40 years old tend to have lower kidney function. The result might be associated with age-related decline of vascular compliance, which in turn affects hypertrophic response.[34,35] Donors who are biologically related to the recipients also show lower kidney functions. However, it is unknown whether the etiology of declining kidney functions in those donors is hereditary.[36,37] In addition to those facts, we have found that donors with higher PWV tend to have lower GFR. Moreover, BMI of over 25 kg/m^2 is correlated with lower GFR pre- and post-nephrectomy. Obese donors have underwent hyperfiltration for years for years in order to meet higher metabolic demand. After nephrectomy, kidney needs to do further compensation, which may result in lower kidney function. Chronic hyperfiltration will also affect changes in blood vessels and blood flow.[38]

Our study has provided evidences about hyperfiltration process as a renal compensatory mechanism in living kidney donor post-nephrectomy (**Figure 4**). The kidney hyperfiltration is characterized by alteration in RI, which reflects altered renal blood flow. A trend of changes in every renal artery, which

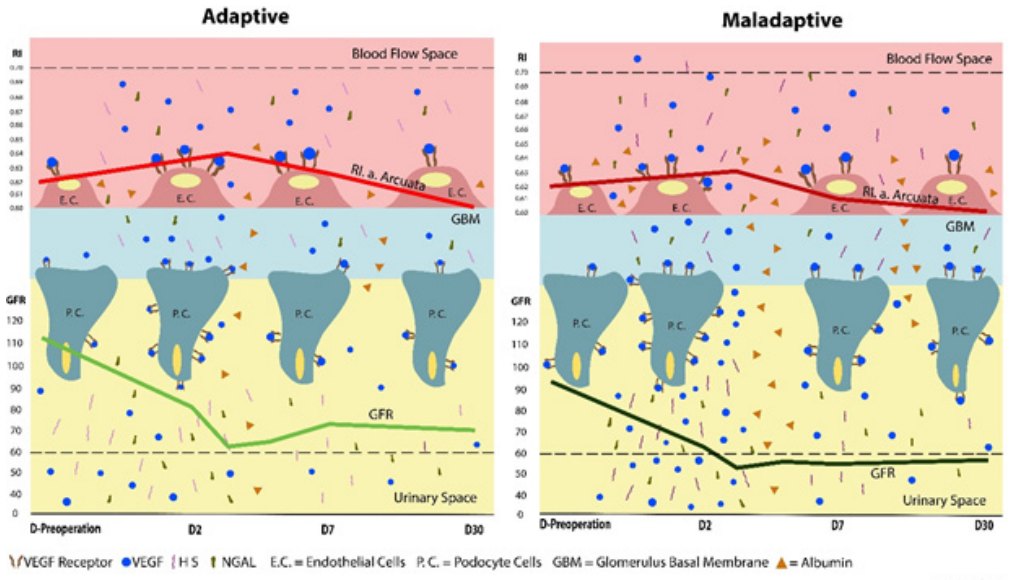

Figure 4. Hyperfiltration is marked by changes in RI, VEGF, HS and NGAL. RI of Arcuate Artery increases more prominently and decline more rapidly in adaptive group (left). VEGF contributes to widening of filtration slit, resulting in worse albuminuria and hence, kidney function. HS promotes VEGF migration from podocytes to endothelial cells. Both VEGF and HS increase dramatically on day 2, and more prominently in maladaptive group. NGAL is produced to a greater extent by maladaptive group, suggesting more severe tubular injury.

flatten back to nearly pre-nephrectomy RI is obvious on the 30th day post-uninephrectomy. Arcuate artery is the most ideal location to assess renal RI in living kidney donation. In addition to that, the kidney hyperfiltration process is also characterized by changes in urinary VEGF level, which reflects compensated kidney hypertrophy. The increase in both urinary NGAL and HS levels may suggest the ischemic and hypoxic condition of remaining kidney tissue due to nephrectomy.

CONCLUSION

The hyperfiltration process does not affect the 30-day post-uninephrectomy kidney function of the donors. The incidence of maladaptive hyperfiltration in kidney living donors within 30 days after nephrectomy is 47.5%. RI, urinary VEGF, NGAL and heparan sulfate proteoglycan levels of donors with adaptive hyperfiltration are not different compared to the results of those with maladaptive hyperfiltration. Several other factors are suggested to have some influences on hyperfiltration process and kidney function. Further studies should include evaluation on the role of genes in hyperfiltration, the role ischemic marker such as KIM-1 and changes in kidney volume within a longer period of monitoring in order to evaluate donors' kidney function and its other related variables.

REFERENCES

1. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J transplant. 2011;11(10):2093-109.
2. Taminato M, Fram D, Grothe C, Pereira RRF, Belasco A, Barbosa D. Prevalence of infection in kidney transplantation from living versus deceased donor: systematic review and meta-analysis. Revista da Escola de Enfermagem da USP. 2015;49:502-7.
3. Gill JS, Tonelli M. Understanding rare adverse outcomes following living kidney donation. JAMA. 2014;311(6):577-9.
4. de Groot IB, Veen JIE, van der Boog PJ, et al. Difference in quality of life, fatigue and societal participation between living and deceased donor kidney transplant recipients. Clinical Transplant. 2013;27(4):E415-E23.
5. Mueller TF, Luyckx VA. The natural history of residual renal function in transplant donors. J Am Soc Nephrol. 2012;23(9):1462-6.
6. Choi KH, Yang SC, Joo DJ, et al. Clinical assessment of renal function stabilization after living donor nephrectomy. Transplantation Proceedings. 2012;44(10):2906-9.
7. Fehrman-Ekholm I, Nordén G, Lennerling A, et al. Incidence of end-stage renal disease among live kidney donors. Transplantation. 2006;82(12):1646-8.
8. Kwon HJ, Kim DH, Jang HR, et al. Predictive factors of renal adaptation after nephrectomy in kidney donors. Transplantation Proceedings. 2017;49(9):1999-2006.
9. Chen Z, Fang J, Li G, et al. Compensatory changes in the retained kidney after nephrectomy in a living related donor. Transplantation Proceedings. 2012;44(10):2901-5.
10. Lenihan CR, Busque S, Derby G, Blouch K, Myers BD, Tan JC. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. J Clin Invest. 2015;125(3):1311-8.
11. Nekouei S, Ahmadnia H, Abedi M, Alamolhodaee MH, Abedi MS. Resistive index of the remaining kidney in allograft kidney donors. Exp Clin Transplant. 2012;10(5):454-7.
12. Kuppe C, Rohlfs W, Grepl M, et al. Inverse correlation between vascular endothelial growth factor back-filtration and capillary filtration pressures. Nephrology Dialysis Transplantation. 2018.
13. Schrijvers BF, Flyvbjerg A, Tilton RG, Rasch R, Lameire NH, De Vriese AS. Pathophysiological role of vascular endothelial growth factor in the remnant kidney. Nephron Experimental nephrology. 2005;101(1):e9-e15.
14. Singer E, Markó L, Paragas N, et al. Neutrophil gelatinase-associated lipocalin: pathophysiology and clinical applications. Acta physiologica (Oxford, England). 2013;207(4):663-72.
15. Stefanidis I, Heintz B, Stöcker G, Mrowka C, Sieberth H-G, Haubeck H-D. Association between heparan sulfate proteoglycan excretion and proteinuria after renal transplantation. J Am Soc Nephrol. 1996;7(12):2670-6.
16. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J. 1999;13(1):9-22.
17. Chen J, Bhattacharya S, Sirota M, et al. Assessment of postdonation outcomes in US living kidney donors using publicly available data sets. JAMA. 2019;2(4):e191851-e.
18. Hart A, Smith J, Skeans M, et al. OPTN/SRTR 2018 Annual Data Report: Kidney. Am J Transplant. 2020;20:20-130.
19. Bloembergen WE, Port FK, Mauger EA, Briggs JP, Leichtman AB. Gender discrepancies in living related renal transplant donors and recipients. J Am Soc Nephrol. 1996;7(8):1139-44.
20. Lim JU, Lee JH, Kim JS, et al. Comparison of World Health Organization and Asia-Pacific body mass index

classifications in COPD patients. Int J Chronic Obstruct Pulmonary Dis. 2017;12:2465.
21. Niemi M, Mandelbrot DA. The outcomes of living kidney donation from medically complex donors: Implications for the donor and the recipient. Curr Transplant Rep. 2014;1(1):1-9.
22. Fesler P, Mourad G, Cailar Gd, Ribstein J, Mimran A. Arterial stiffness: an independent determinant of adaptive glomerular hyperfiltration after kidney donation. Am J Physiol - Renal Physiol. 2015;308(6):F567-F71.
23. Yoon Y, Lee H, Na J, Han W. Prospective assessment of urinary NGAL in living kidney donors: toward understanding differences between chronic kidney diseases of surgical and medical origin. BJU Int. 2018.
24. Bohlouli A, Tarzamni MK, Zomorrodi A, Abdollahifard S, Hashemi B, Nezami N. Postnephrectomy changes in Doppler indexes of remnant kidney in unrelated kidney donors. Urol J. 2009;6(3):194-8.
25. Shokeir AA, Abubieh EA, Dawaba M, El-Azab M. Resistive index of the solitary kidney: a clinical study of normal values. J Urol. 2003;170(2):377-9.
26. Sigmon DH, Gonzalez-Feldman E, Cavasin MA, Potter DAL, Beierwaltes WH. Role of Nitric Oxide in the renal hemodynamic response to unilateral nephrectomy. J Am Soc Nephrol. 2004;15(6):1413-20.
27. Valdivielso JM, Pérez-Barriocanal F, García-Estañ J, López-Novoa JM. Role of nitric oxide in the early renal hemodynamic response after unilateral nephrectomy. Am J Physiol-Regulatory, Integr Compar Physiol. 1999;276(6):R1718-R23.
28. Molema G, Aird WC, editors. Vascular heterogeneity in the kidney. Seminars in nephrology. New York: Elsevier; 2012.
29. Ow CP, Ngo JP, Ullah MM, Hilliard LM, Evans RG. Renal hypoxia in kidney disease: cause or consequence? Acta Physiologica. 2018;222(4):e12999.
30. Kanellis J, Mudge SJ, Fraser S, Katerelos M, Power DA. Redistribution of cytoplasmic VEGF to the basolateral aspect of renal tubular cells in ischemia-reperfusion injury. Kidney Int. 2000;57(6):2445-56.
31. El Awad B, Kreft B, Wolber E-M, et al. Hypoxia and interleukin-1β stimulate vascular endothelial growth factor production in human proximal tubular cells. Kidney Int. 2000;58(1):43-50.
32. Flyvbjerg A, Schrijvers BF, De Vriese AS, Tilton RG, Rasch R. Compensatory glomerular growth after unilateral nephrectomy is VEGF dependent. Am J Physiol-Endocrinol Metabolism. 2002;283(2):E362-E6.
33. Yoon YE, Cho YI, Kim SY, et al. Plasma Neutrophil Gelatinase-associated Lipoprotein in living kidney and donors. Transplantation Proceedings. 2016;48(3):738-41.
34. Jeon HG, Lee SR, Joo DJ, et al. Predictors of kidney volume change and delayed kidney function recovery after donor nephrectomy. J Urol. 2010;184(3):1057-63.
35. Konno O, Nakamura Y, Yokoyama T, Kihara Y, Iwamoto H, Kawachi S, editors. Postoperative compensatory changes and blood flow parameter of the preserved kidney in elderly living related donors evaluated by Doppler ultrasonography. Transplantation proceedings; 2016: Elsevier.
36. Skrunes R, Svarstad E, Reisæter AV, Vikse BE. Familial clustering of ESRD in the Norwegian population. Clin J Am Soc Nephrol. 2014;9(10):1692-700.
37. Fallahzadeh MK, Jafari L, Roozbeh J, et al. Comparison of health status and quality of life of related versus paid unrelated living kidney donors. Am J Transplant. 2013;13(12):3210-4.
38. Chang AR, Zafar W, Grams ME. Kidney function in obesity—challenges in indexing and estimation. Advance Chronic Kidney Dis. 2018;25(1):31-40.

Report of Two COVID-19 ARDS (CARDS) Cases Who Survived without Intubation and Mechanical Ventilation

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ABSTRAK

Manifestasi klinis kritis COVID-19 adalah Acute Respiratory Distress Syndrome (ARDS) yang memerlukan intubasi dan ventilasi mekanik dan terjadi pada sekitar 2,3% kasus. Sekitar 94% kasus COVID-19 dengan ventilator ini berakhir dengan kematian. Serial kasus ini melaporkan dua pasien confirmed COVID-19 yang sudah memenuhi kriteria intubasi dan ventilasi mekanik namun tidak dilakukan. Pada perjalanan penyakitnya kedua pasien mengalami perbaikan klinis dan sembuh. Hal yang mungkin dapat menjelaskan adalah karena terdapat perbedaan antara COVID-19 ARDS (CARDS) dengan ARDS tipikal atau klasik. CARDS terbagi menjadi 2 fenotip tipe L (Low Elastance) dan tipe H (High Elastance). Perbedaan fenotip ini membedakan pula patofisiologi dan tatalaksana klinis, dan cara untuk membedakannya antara lain dengan CT scan thorax. Serial kasus ini menekankan pentingnya pemahaman terhadap fenotip COVID-19 agar klinisi dapat memberikan tatalaksana terapi dengan lebih tepat, sekaligus menekankan pentingnya ketersediaan CT scan pada fasilitas kesehatan yang menatalaksana COVID-19.

Kata kunci: *COVID-19, ARDS, CARDS, ventilasi mekanik, CT-scan thorax.*

ABSTRACT

The most severe clinical feature of COVID-19 is Acute Respiratory Distress Syndrome (ARDS) which requires intubation and mechanical ventilation and it occurs in approximately 2.3% of cases. About 94% of these cases end in death. This case series report two confirmed COVID-19 patients who had met criteria of intubation and mechanical ventilation, but not performed to them. Both patients experienced clinical improvement and recovery. This is probably due to differences of COVID-19 ARDS (CARDS) with typical or classic ARDS. CARDS is divided into two phenotypes of type L (Low Elastance) and type H (High Elastance). These different phenotypic also distinguish subsequent pathophysiology and clinical management. These phenotype can be differentiated by chest CT scan. This case series emphasizes the importance of understanding this phenotype so that clinicians can provide more appropriate treatment management and also availability of CT scans in health facilities that manage COVID -19.

Keywords: *COVID-19, ARDS, CARDS, mechanical ventilation, thorax CT-scan.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a new coronavirus and was first reported in Wuhan, China, in December 2019. COVID-19 disease has clinical variations ranging from mild or even without symptoms to critical conditions require an intensive care unit. About 14% of COVID-19 cases develop severe cases and 5% may require intensive care units and developed Acute Respiratory Distress Syndrome (ARDS), sepsis, septic shock, multiorgan failure, Acute Kidney Injury and cardiac injury.[1] ARDS complicates in around 2.3%, and 94 of % of them ended in death.[2,3]

We describe two cases of COVID-19 that met the Kigali-Modified ARDS Berlin criteria. They also met indications of intubation and mechanical ventilation but they were not intubated, however both cases experienced clinical improvement and they were declared cured after two negative RT-PCR results.

CASE ILLUSTRATION

Case 1

A 46-year-old man came to hospital due to shortness of breath (SOB) for seven days which worsened in the previous two days. He also complained of cough, nasal congestion, and had a history of fever six days prior to the visit lasting for two days. He had a close contact with confirmed COVID-19 patient at a religious event. There was no history of hypertension, diabetes, heart disease or chronic lung disease.

Patient was alert, blood pressure 120/70 mmHg, pulse 84 beats per minute, respiratory rate 24 breaths per minute, temperature 36.7^{0}C. Body Mass Index (BMI) 24.7 kg/m^2. Crackles were present in both hemithorax. Other physical examination results were within normal limit.

Laboratory results showed Hb 14.5 g/dL, Ht 42.5%, white blood cell count 11,810/mm^3, platelet count 302,000/mm^3, basophil 0%, eosinophils 0%, stab neutrophils 0%, segmented neutrophils 91%, lymphocytes 5%, monocytes 4%, Total Lymphocytes Count (TLC) 590/mm^3, blood sugar 134 mg/dL, serum ureum 68 mg/dL, serum creatinine 1.19 mg/dL, potassium 4.2 mEg/L, blood gas analysis pH 7.424, pCO2 27.8 mmHg, pO2 127.9 mmHg, HCO3 18.4 mmol/liter, BE -3.9 mmol/liter, SaO2 98.5%, partial pressure of oxygen/ fraction of inspired oxygen (P/F) ratio 426, with oxygen 3 liters/minute. Chest X Ray (CXR) showed peripheral infiltrate sugestive for pnemonia and slight cardiomegaly.

The diagnosis of Community Acquired Pneumoniae (CAP) was made and the patient was under investigation for COVID 19.

The patient was treated in isolation ward with supplementary oxygen 3 l/min (lpm), empirical antibiotics ceftriaxone 2x1 grams and azithromycin 1x500 mg, N-Acetylcystein 3x400 mg and oseltamivir 2x150 mg to cover

Table 1. Clinical course of case 1.

Day	Symptoms	BP	Pulse	RR	Temp	SpO2/ FiO2
01	Cough	116/73	96	24	37.0	342
07	Dyspnea	123/80	78	24	36.8	156
08	Dyspnea	130/90	96	28	36.4	160
09	Dyspnea, cough	130/80	96	26	36.3	156
10	Dyspnea, cough	120/80	80	28	36.4	101
11	Dyspnea, cough	125/70	84	32	36.8	101
12	Dyspnea, cough	117/75	88	30	36.2	97
23	None	110/70	86	20	36.4	350
48	None	126/76	80	20	36.4	490

Table 2. Laboratory data during hospitalization.

Day	Leucocyte	TLC	CRP	PC	Ferritin	RT-PCR
01	11.810	590				POS
07	9.170	730				
08	10.550	950	6.27			POS
12	7.060	1060				
13	7.020	1470				
14	6.240	1310				
18			0.22	0.3		
19			0.26			
21	7.200	1944				POS
24	5.000	2200				
27			0.11		797	
33			0.19		833	
44	6.650	2261				NEG

TLC (Total Lymphocyte Count), CRP (C Reactive Protein), PC (Procalcitonin)

the influenza empirically. Chloroquine 2x500 mg and paracetamol 3x500 mg orally. Three days later antibiotic was changed to 3x1 gram meropenem and 2x400 mg ciprofloxacin intravenously. Then, on the 6th day of treatment the patient received 2x1 grams of vancomycin and UFH 3x5000 U was also given.

On day 7 SOB was worsening, oxygen saturation dropped to 94% with Simple Mask 10 lpm (**Table 1**). CXR showed progressive infiltrate (**Figure 1**). RT-PCR result was positive For SARS-CoV-2 infection. Care plans included transferring the patient to the isolation ICU and considering to be intubated. At that time, the patient could communicate appropriately and refused intubation. Subsequently, patient's condition continued to worsen for six days with lowest SpO2 92% with Non-Rebreathing Mask (NRM) 12 lpm and lowest SpO2/FiO2 97.

On the 14th day, the patient clinical condition began to improved. Decreased SOB, still in NRM 7 lpm oxygen, SpO2 92% and P/F ratio increases to 245. From the 14th day onwards until 45th day of treatment improvement continue and RT-PCR was negative twice, the P/F ratio 381 without oxygen supplementation, CXR obtained improved infiltrate. Because of limited resources, CT Scan examination could only be done once immediately before discharge and a ground glass opacity was still obtained (**Figure 2**).

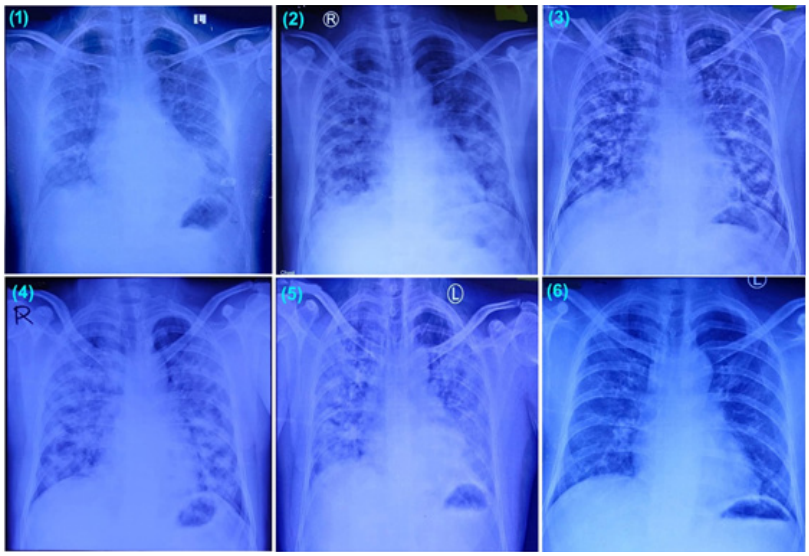

Figure 1. Serial chest X ray of case 1 from day 1 until before hospital discharge.

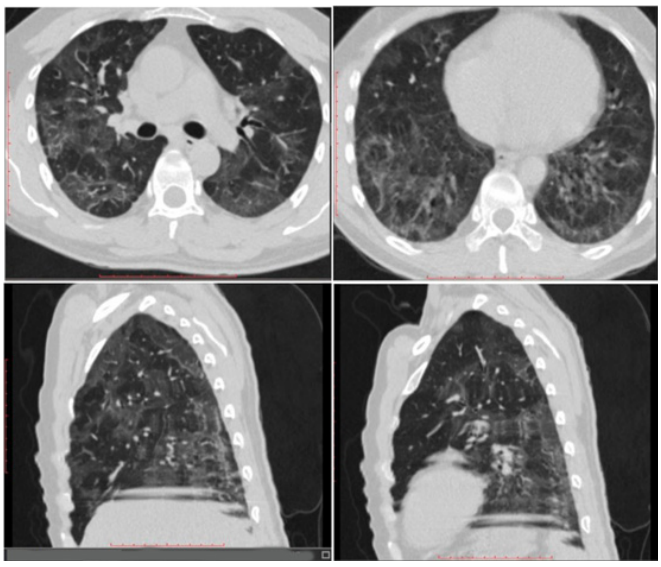

Figure 2. CT scan thorax case 1 on 57th day of illness.

Case 2

A 64-year-old man came to hospital due to shortness of breath for seven days and worsening in the last three days, cough with yellowish phlegm and cold. There was no fever, sore throat and diarrhea. He already had a history of dyspnea on exertion since 3 months ago. Three months earlier he underwent cardiac catheterization and stent placement.

Routine medications are aspirin, bisoprolol, furosemide and atorvastatin. He had Diabetes Mellitus (DM) for 14 years and treated with metformin. He is an active smoker and had a history of high cholesterol. He had no history of traveling outside city. There was no history of contact with COVID 19 cases.

The patient appeared seriously ill but fully awake, BP 130/80 mmHg, pulse 118 beats per minute, respiratory rate 32 breaths per minute, temperature 36.7^{o}C, ratio SpO2/FiO2 was 98 and BMI 28.6 kg/m^{2}. Coarse crackle was heard at right hemithorax. He had slight cardiomegaly and other findings were within normal limit.

The laboratory data were Hb 12.1 g/dL, Ht 33.7%, white cell count 9.170/mm^{3}, platelet count 274,000/mm^{3}, basophils 0%, eosinophils 0%, band neutrophils 2%, segmented neutrophils 73%, lymphocytes 16%, monocytes 9%, TLC 1470/mm^{3}, RBS 240 mg/dL, serum ureum 38 mg/dL, serum creatinine 1.19 mg/dL, sodium 132 mEq/L, potassium 4.7 mEq/L, pH 7.551, pCO2 27.1 mmHg, pO2 103.2 mmHg, HCO3 21.9 mmol/l, BE 0.5 mmol/L, SaO2 97.7% and P/F ratio 149, Electrocardiography suggested sinus rhythm, and CXR showed bilateral peripheral opacity with slight cardiomegaly.

Initial diagnosis were patient under investigation (PDP) COVID-19 with respiratory insufficiency, DM type 2 with diabetic neuropathy, diabetic kidney disease, coronary arterial disease one vessel disease post primary coronary (one vessel disease post primary coronary intervention on left anterior descending artery), heart failure, hypertension and overweight.

Patient received care in isolation ward, oxygen 10 lpm NRM, NaCl 0.9% 1000 cc/24 hours, ceftriaxone 2x1 gram and levofloxacin 1x750 mg intravenously, oseltamivir 2x150 mg, chloroquine 2x500 mg, ISDN 1x5 mg sublingual, aspilets 1x81 mg, bisoprolol 1x5 mg, ramipril 1x1.25 mg, atorvastatin 1x40 mg, N-acetylcysteine 3x200 mg and furosemide 1x40 mg orally.

Since the first day of hospitalization until day 8, the patient experienced clinical deterioration (**Table 3**), worsening SOB, respiratory rate 32 breaths per minute, lowest P/F ratio 149, and CXR suggested increased infiltrates (**Figure 3**).

Table 3. Clinical course of case 2.

Day	Symptoms	BP	Pulse	RR	Temp	SpO2/ FiO2
01	Dyspnea, cough	130/80	112	32	36.7	98
02	Dyspnea, cough	129/80	100	30	36.4	98
03	Dyspnea, cough	114/72	94	28	36.6	100
04	Dyspnea, cough	130/80	84	24	36.3	103
05	Dyspnea	127/82	93	26	36.0	123
06	Dyspnea	120/70	100	24	36.9	124
07	Dyspnea	123/85	100	26	36.2	104
08	Dyspnea	130/90	96	24	36.4	192
09	Dyspnea, cough	130/80	96	26	36.3	161
17	Dyspnea	125/83	82	22	36.2	269
21	Cough	128/76	87	20	36.2	400
22	None	127/75	86	20	36.4	346
32	None	110/70	80	20	36.2	490

Table 4. Laboratory data of case 2 during hospitalization.

Day	Leucocyte	TLC	CRP	PC	Ferritin	RT-PCR
01	9.170	1470				
02	8.670	1210				POS
05	10.001	1400				
07	10.730	1610				
08	8.580	1460	6.75			
09	8.810	1321			1378.5	
12						NEG
13			7.31			
14			5.68		1628	
16	6.970	1742				
18	11.580	1968	13.09		1692.2	
19	9.430	1980				NEG
20	9.310	2606				
23	5.980	1973				
31	6.800	1900	0.53			
35	7.280	2402				

TLC (Total Lymphocyte Count), CRP (C Reactive Protein), PC (Procalcitonin)

RT-PCR result which obtained later was positive.

Since hospital admission, the patient was planned to be treated in isolation ICU, for intubation and mechanical ventilation but he refused. Fortunately from ninth day of treatment, clinical condition was improved, on the thirty fifth day of care the patient was declared cured after two negative RT-PCR results. Before discharged, the patient underwent CT scan of the thorax without contrast, and the result suggested persistence of ground glass opacity (**Figure 4**).

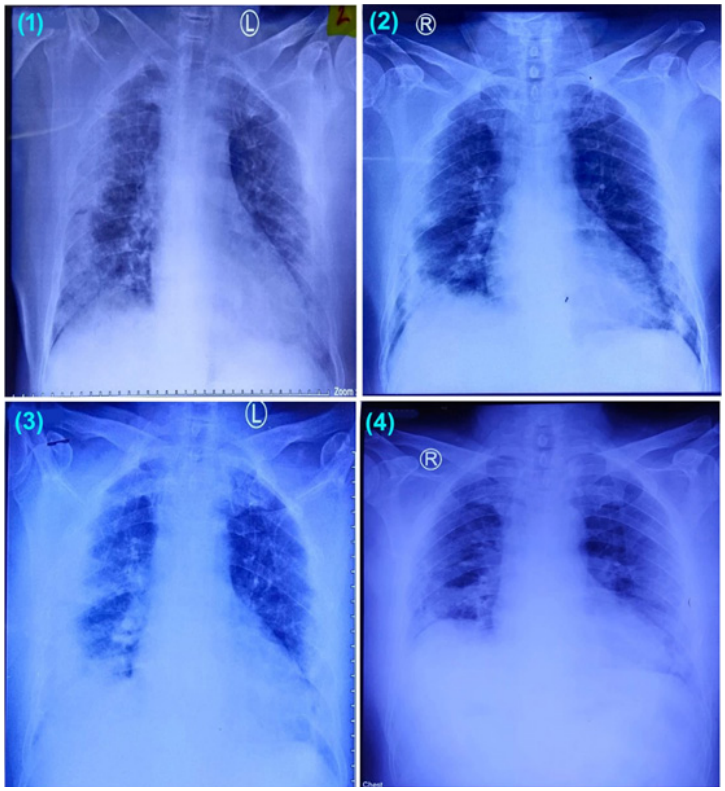

Figure 3. Serial chest X ray of case 2.

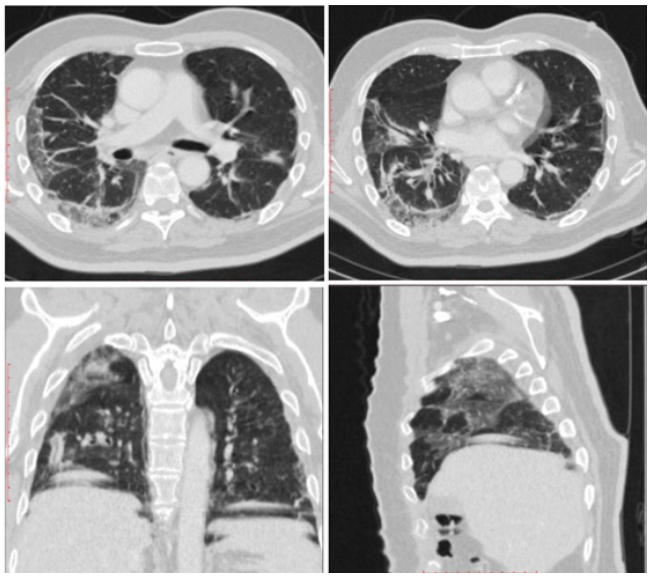

Figure 4. CT scan thorax case 2 on 46th day of illness.

DISCUSSION

In case 1, clinical deterioration occurred between 7th to 13th day hospitalization (day 14th to 20th from onset), SOB worsen, RR 30/ min, lowest SpO2 92% with NRM 12 lpm, lowest SpO2/FiO2 ratio 97. CXR showed progressive infiltrates (**Figure 1**). While in case 2 clinical deterioration occurred from the first to eighth day of hospitalization (day 7th to 15th from onset), highest RR 32 times/min with the lowest SpO2/FiO2 ratio 98. CXR series showed increase infiltrate (**Figure 3**).

Based on Kigali modification of the Berlin criteria in 20174 cases 1 and 2 fall in ARDS conditions. In Kigali modification ARDS was defined without the need of positive end-expiratory pressure, with the presence of bilateral opacities of chest radiograph or lung ultrasound and hypoxia was defined with a cutoff of SpO2/ FiO2 ratio $\leq$ 315.[1,4]

According to the criteria established by Meng et al.[5] on the seventh day of hospitlization in case 1 and the first day in case 2 already met the criteria for intubation. But intubation were not performed. If these patients were not mechanically ventilated, according to pathway proposed by Vincent et al.[6] both cases are in the death path. In fact, both cases were improved and survived without intubation and mechanical ventilation.

There is an assumption that ARDS in COVID-19 (CARDS) is different with classic ARDS.[7,8] Gattinoni et al.[7] suggested that COVID-19 ARDS had two different phenotypes, namely type L and type H.

CARDS type L phenotype characteristics: (1) typical viral pneumonitis at initial presentation; (2) increase infiltrate but only in limited area, at first usually characterized by a pattern of ground glass on CT and more likely as interstitial edema rather than alveolar. Many patients do not complain SOB despite poor oxygenation conditions; (3) hypoxemia with good CO2 clearance (type 1 respiratory failure); (4) low in: (a) elastance (high compliance), (b) ventilation to perfusion ratio V/Q due to hypoxic induced vasoconstriction abnormalities (vasoplegia), (c) recruitability (poor response to PEEP and proning), (5) implications of these: (a) can avoid the use of mechanical ventilation with more conservative oxygen supplementation; (b) responsive to pulmonary vasodilators (for example inhalation of nitric oxide); (c) many experience clinical improvement at this stage, however some are deteriorating and transitioning to type H.

Type H CARDS has the following characteristics: (1) continuation of the worsening of COVID-19 with a classic picture of ARDS; (2) hypoxemia that occurs with impaired CO2 clearance (type 1 and/ or type 2 respiratory failure); (3) widespread consolidation of the chest CT scan (extensive CT consolidations), increased lung mass; (4) high in: (a) elastance (low compliance), (b) V/Q matching, (d) recruitability (responsive to PEEP and proning); (5) implications: It is better to use mechanical ventilation and ARDS therapy as usual. CT scan be used to distinguish COVID-19 ARDS phenotype type L and type H. Where Type H present as typical picture of ARDS.[7]

Both cases appeared to have type L CARDS, which means that their lungs were still in high compliance state and type L patients could experience improvement without mechanical ventilation. But this assumption could not be confirmed, because when both cases experienced clinical deterioration, CT scan could not be ordered. This was due inavailability of CT scan machine intended specially for infectious cases of COVID-19 in our hospital.[7]

There are several possible explanations for why these two cases recovered from type L instead progress to type H which is a typical picture of ARDS.

Siddiqi et al.[9] divided the course of COVID-19 into three stages: (1) Stage I or the initial phase of infection. This stage can be asymptomatic or non specific mild symptoms, such as malaise, fever and dry cough. During this period the virus replicates in the host, especially in the respiratory system. The virus binds to ACE 2 receptors in human cells, these receptors are found in the human lung, small intestinal epithelium and blood vessel endothelium; (2) Stage II or pulmonary phase. At this stage patients developed respiratory symptoms due to local inflammation of the lungs. Viral pneumonia occurs with symptoms of cough,

fever and possible hypoxia, PaO2/FiO2<300. CXR or CT scan shows the presence of bilateral infiltrate or ground glass opacity; (3) Stage III or hyperinflammatory phase in this stage, markers of systemic inflammation appear to be elevated. Inflammatory cytokines and biomarkers such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C reactive protein, ferritin, and D-dimer are significantly elevated in those patients with more severe disease.[9] This condition is also known as cytokine storm.[10,11] At this stage, shock, vasoplegia, respiratory failure and even cardiopulmonary collapse are discernable.[9]

In COVID-19, cytokine storm is a key factor in the process of ARDS. Serum cytokines increase significantly in patients with ARDS, and high serum cytokine levels correlate with high mortality.[12]

Cytokine Release Syndrome (CRS) had characteristic signs and symptoms: (1) continuous high fever; (2) tissue and organ damage caused by immune reactions related to cytokines and coagulation disorders; (3) significant increase in IL-6 cytokines in the blood; (4) decreased circulation of CD4, CD8 and NK cells in the blood. CRS conditions on COVID-19 often occur between day 7 to day 16. The best marker to evaluate progress and decline of this CRS is IL-6 level. Several other markers including CRP, LDH and ferritin can also be used, their kinetic almost similar with IL-6.[13-15]

A cohort study conducted by Liu, et al.[15] provides a description of the kinetic changes in cytokine levels such as IL-2, IL-4, IL-6, IL-10, IFN-g and TNF-a. In mild and severe COVID-19 patients, Cytokine levels reached their peak levels on the sixth day after the onset of illness except IL-6. IL-6 and IL-10 could continuously increase in severe COVID-19, IL-6 levels would begin to decrease on the sixteenth day after the onset of the disease, while IL-10 had reached its lowest thirteen days after onset disease. Increased serum IL-2 and IFN-g levels in severe COVID-19 only appeared 4-6 days after disease onset. All cytokines decreased both in severe and mild patients on the 16th day after disease onset.[16,17]

Other study showed that on the third day of hospitalization, severe COVID-19 patients had high levels of IL-6, CRP, and LDH. Then the levels began to fall on days seven to nine in patients with moderate and severe COVID-19.[18] So it could be assumed that CRS could be occurred between day three of hospitalization to sixteen days after symptom onset.16 Higher levels of IL-6 also associated with increased ground glass opacity in the CT scan of the thorax of severe COVID-19 patients.[13]

When their clinical manifestation deteriorate, both cases were between day 7-16 after onset of illness and it was likely that they were at stage III COVID-19 (hyperinflammation stage) which was characterized by severe symptoms and ARDS. So CRS was currently underway. Although it could not be proven with IL-6 levels but there were CRP and ferritin data were available even though the test was not precisely done at the same time as the disease course when CRS occurred.

In case 1, at day seventh of hospitalization, CRP level was high 6.27 mg/dL (normal CRP<0.03 mg/dL). Serial CXR of the patient also showed an increase in infiltrate (**Figure 1**). Then on fourteenth day CRP levels decreased by 0.57 mg/dL, in line with the patient's clinical condition which showed improvement (**Table 1**). In case 2, CRP and ferritin levels on the 8th day were high, i.e. 6.75 mg/dL and 1378.5 ng/ml (normal ferritin 22-232 ng/ml). In serial CXR, infiltrates were also increase (**Figure 3**). On the fourteenth day, the CRP and ferritin levels of the patient were still high at 13.09 mg/dL and 1692 ng/ml. On day twenty eighth when clinical condition already improved, CRP levels fell to 0.53 mg/dL. These data suggested that CRS occurred when both cases experienced worsening clinical condition.

Ventilation management of type L and H CARDS is quite different. In the type L phenotype, the initial steps to restore hypoxemia are: (1) increase FiO2; noninvasive options such as High Flow Nasal Cannula (HFNC), Continuous Positive Airway Pressure (CPAP) or with Non-Invasive Ventilation (NIV); (2) estimate work of breathing; (3) increase PEEP wisely because it has the potential to reduce

pleural pressure swings so that the phenotype may be altered; (4) conditioning patient in prone position; (5) if respiratory distress present intubation may be able to avoid/ limit progression to the H type phenotype.[7]

Treatment to both cases that probably gave positive impact include ventilation with adequate FiO2 even though it was given with conventional masks (SM and NRM). This adequate administration of oxygenation did not make intrathoracic pressure became more negative and increasing in tidal volume while in spontaneous breathing. The combination of intrathoracic negative pressure and increased lung permeability due to inflammation was thought to be the cause of interstitial pulmonary edema. This phenomenon was referred to as Patient-Self Inflicted Lung Injury (P-SILI).[17]

Although still controversial, but there were probability benefit of medication given to both cases. Several studies have shown chloroquine and hydroxy chloroquine could reduce the production of various proinflammatory cytokines, such as IL-1, IL-6, interferon-α and tumor necrosis factor, which are involved in cytokine storm, reduce the occurrence of exacerbation of pneumonia, and increase the possibility of negative conversion to COVID virus.[12,18]

The course of the disease of this two cases we presented supports the different pathophysiological concepts between ARDS that occur in COVID-19 (CARDS) and classic ARDS. It is crucial to understand the concept of the pathophysiology of L and H phenotype and to apply it in the management of patients with COVID-19 ARDS

CONCLUSION

Understanding the pathophysiology is very important for appropriate and adequate management. The underlying mechanism of CARDS phenomenon is Cytokine Relase Syndrome (CRS) which occurs around seven to sixteen days from the onset of symptoms. CARDS is quite different from classical ARDS. Type L CARDS does not exactly the same as ARDS although it meets the ARDS criteria according to the Kigali modification of the Berlin criteria, whereas the H COVID-19 phenotype may be the clasic ARDS. Type L and H CARDS patients can be identified using CT scan. This emphasizes the importance of the availability of CT scan examinations in health facilities that manage COVID-19.

REFERENCES

1. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Interim Guidance 13 Maret 2020.
2. WHO. Coronavirus disease 2019 (COVID019) situation report - 59. Accessed March 20, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200319-sitrep-59-covid-19.pdf.
3. Yao W, Wang T, Jiang B, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international recommendations. Brit J Anaesthesia Elsevier. 2020; 11(2):3-4.
4. Riviello ED, Buregeya E, Twagirumugabe T. Diagnosing acute respiratory distress syndrome in resource limited settings: the Kigali modification of the Berlin definition. Curr Opin Crit Care. 2017;23:18-23.
5. Meng L, Qiu H, Wan L, et al. Intubation and ventilation amid the COVID-19 outbreak. Anesthesiol. 2020; 16(6):3-8.
6. Vincent J, Taccone F, et al. Understanding pathways to death in patients with COVID-19. Lancet Respir Med. 2020;3.
7. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Medicine. 2020;3.
8. Woods A. COVID-19 not your "typical" ARDS. Lippincott 2020 DIkutip dari https://wwwnursingcentercom/ncblog/april-2020/covid-19-not-your-typical-ards.
9. Siddiqi H, Mehra M, et al. COVID-19 illness in native and immunosuppressed state. J Heart Lung Transplant. 2020.
10. Cao X. COVID-19: Immunopathology and its implications for theraphy. Nature Rev Immunol. 2020; 20.
11. Henderson, Canna S, Schulert G, et al. On the alert for cytokine storm: Immunopathology in COVID-19. Research Gate 2020.
12. Ye Q, Wang B, Mao J, et al. Cytokine storm in COVID-19 and treatment. Elsevier 2020.
13. Wenjun W, Xiaoqing L, Sipei W, et al. The definition and risk of cytokine release syndrome-like in 11 COVID-19 infected pneumonia critically ill patients: disease characteristics and retrospective analysis. MedRxiv 2020.
14. Diamanti A, Rosado M, Pioli C, et al. Cytokine release syndrome in COVID-19 patients, a new scenario for an old concern: the fragile balance between infections and autoimmunity. Int J Mol Sci. 2020;21.

15. Liu J, Li S, Liu JJ, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. Elsevier. 2020;55.
16. Yuan J, Zou R, Zeng L, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflammation Res. 2020;69.
17. Marini J, Gattinoni L. Management of COVID-19 respiratory distress. JAMA. 2020 Published online April 24, 2020 doi:101001/jama20206825.
18. Zhao M. Cytokine storm and immunomudulatory theraphy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. Elsevier. 2020;20.

Diarrhea as an Early and Predominant Manifestation of Coronavirus Disease 2019 (COVID-19): A Case Report

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ABSTRAK

Coronavirus disease 2019 (COVID-19) merupakan salah satu penyakit infeksi baru yang dengan sangat cepat menyebar hingga WHO menyatakannya sebagai penyakit pandemik yang mendunia. Gejala klinis utama pada pasien COVID-19 adalah batuk dan demam, namun diare dapat menjadi salah satu gejala awal. Laporan kasus ini menerangkan seorang pasien yang datang dengan keluhan diare tanpa demam yang terkonfirmasi positif COVID-19 dalam perawatan. Adanya gejala awal yang tidak spesifik menuntut tenaga kesehatan untuk lebih waspada dalam menegakkan diagnosis COVID-19.

Kata kunci: *COVID-19, SARS-Cov-2, diare, manifestasi awal, Indonesia.*

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a new infectious disease that spreads very rapidly and therefore, WHO has declared it as a global pandemic disease. The main clinical symptoms found in COVID-19 patients are cough and fever; however, in some cases, diarrhea can be one of the early symptoms. The present case report describes a patient who came with a complaint of diarrhea without fever and she was later confirmed to be positive for COVID-19 during hospitalization. The presence of unspecified initial symptoms calls for greater vigilance from health workers in establishing diagnosis patients with COVID-19.

Keywords: *COVID-19, SARS-Cov-2, diarrhea, early manifestations, Indonesia.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel infectious disease emerging at the end of 2019. It is caused by Severe Acure Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which first appears in Wuhan, China and spreads extremely fast worldwide; therefore, WHO declares it as a global pandemic disease. In such period of time, it spreads rapidly including in Indonesia. The first detected case in Indonesia was found in early March 2020. By the early of May 2020, there are over 3 million confirmed cases with more than 250 thousands of deaths worldwide.[1]

In Indonesia, based on data provided by the COVID 19 Mitigation Task Force, there are 12,776 confirmed cases by the early May with 930 deaths of all areas in the country.[2] The most

common early manifestations of the disease are fever and cough; however, some uncommon manifestation may also be found, which calls for extreme caution from medical health workers. One of the uncommon manifestations is gastrointestinal manifestation in the form of diarrhea.

In tropical country, where diarrhea is a common complaint found in the community; however, during the time of pandemic, COVID 19 should become one of differential diagnosis in patients with early symptom of diarrhea. Furthermore, it should be followed by a thorough directed history taking and necessary laboratory workup in order to establish or to exclude the diagnosis. In our case report, we are going to present a case of patient with early and predominant manifestation of diarrhea without fever that was later diagnosed with COVID 19. Another case reports and epidemiological data have shown that symptoms of diarrhea can be found in the course of COVID-19 disease. Case reports from the first COVID-19 patient in the United States, showed that COVID-19 patients had diarrhea symptoms. However, this patient admitted with respiratory problems accompanied by fever, whereas diarrhea appeared on the second day of treatment at the hospital.[3] Other case reports in Qatar and China showed similar cases. Diarrhea and abdominal pain are found as presenting symptoms, but later, high fever and worsening respiratory symptoms develop.[4,5] What makes this report interesting is that patients present with the main symptoms of diarrhea without fever. Even throughout the course of the disease fever was not found. In these patients the signs and symptoms of the respiratory tract throughout the course of the disease are also mild, including the X-ray picture that is not typical.

By studying the case, we expect that it may increase greater awareness and knowledge on manifestations of COVID19 disease

CASE ILLUSTRATION

There was a 72-year-old woman with a complaint of diarrhea for 3 days prior to her hospitalization. The patient also had a complaint of minimal infrequent cough and she felt aches and pain all over her body. History of fever was denied by the patient. She came for treatment after knowing that her sister had been tested positive with COVID-19 and her husband had the same symptoms with her sister's. Afterwards, the patient received treatment in an isolation ward. Her initial blood pressure was 144/70 mmHg with pulse rate of 73 beats/minute, respiratory rate of 20 times/minute and her body temperature was 36.5 ^{o}C.

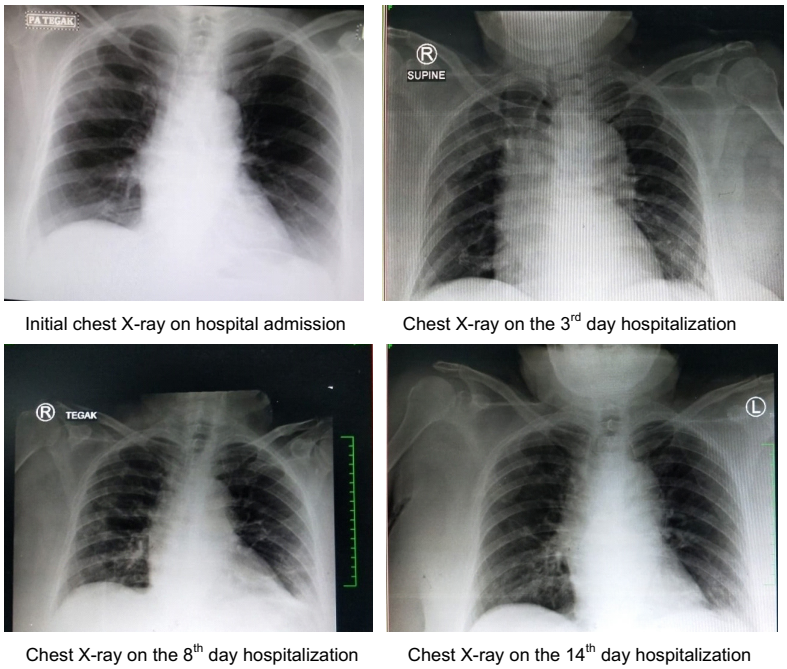
The early laboratory workup showed hemoglobin level (15.7 g/dL), hematocrit (46%), leukocytes (4200/uL), platelet counts (171000/ul) and lymphocytes (30%). Biochemical blood examination revealed AST (37 U/l), ALT (27 U/l), ureum (25 mg/dL), creatinine (1.3 mg/dL) levels and random blood glucose level (RBG) of 137 g/dL. In the early phase of hospitalization, her C-Reactive Protein (CRP) level was 1.5 mg/dL; while her procalcitonin level was 0.11 ng/mL and D-dimer level was 600 ng/mL. On the first day of hospitalization, the patient complained of reduced appetite; however, she denied having fever and short of breath, but she had cough once in a while. Her initial chest X-ray result revealed minimal infiltrate on her left lung. On the third day, the complaint of liquid stool had disappeared, but she still had loss of appetite. The laboratory workup on the third day of hospitalization showed that her CRP level increased to 2.2 mg/dL. The chest X-ray examination was repeated and there was infiltrate at the base of her left lung. On the 6th day, the patient complained about diarrhea again as many as 4 to 6 times of bowel movement daily with liquid stool. She also had a complaint of infrequent cough.

On the 6th day, the laboratory workup was repeated showing the following results of hemoglobin level (11.8 g/dL), hematocrit (37%), leukocyte (4600/uL), platelet count (122000/ul), netrophils (72%) and lymphocytes (18%). The biochemical blood examination revealed increased AST level into 80 U/l and ALT level of 50 U/l; moreover, her CRP level also increased into 4.8 mg/dL.

On the 8th day of hospitalization, she had more frequent cough without dyspnea, but there was no fever. Her vital sign was still

Tabel 1. Laboratory examination

Laboratory exm	Day 1	Day 3	Day 6	Day 8	Day 11
Hb (g/dl)	15.7		11.8	13.2	13.7
Leukocytes count (/uL)	4200		4600	5900	3700
Platelet count (/ul)	171.000		122.000	123.000	146.000
Lymphocytes (%)			18	10	18
AST (U/l)	37		80		
ALT(U/l)	27		50		
Ur (mg/dl)	25				
Cr (mg/dl)	1.3				
CRP (mg/dl)	1.5	2.2	4.8	11.1	5.7
Procalcitonin (ng/ml)	0.11				
DDIMER (ng/ml)	600			1900	



Initial chest X-ray on hospital admission

Chest X-ray on the 3rd day hospitalization

Chest X-ray on the 8th day hospitalization

Chest X-ray on the 14th day hospitalization

Figure 1. Initial chest X-ray on the day hospitalization.

normal. The patient still complained of diarrhea with liquid stool. Another laboratory workup was performed with the following results, i.e. hemoglobin level (13.2 g/dL), hematocrit (39%), leukocytes (5900/uL), platelet count (123000/ul) and neutrophils (77%) and lymphocytes (10%) . The CRP level increased into 11.1 mg/dL and D-dimer level was 1900 ng/mL. At the time, chest X-ray examination was repeated revealing an aggravated infiltrate at the base of both lungs (bilateral basal lung infiltrate).

On the 10th and 11th day of hospitalization, the clinical condition was improved. The patient had no cough, no short of breath and no diarrhea as well as no fever. Another laboratory workup was carried out with the results of hemoglobin level (13.7 g/dL), hematocrit (42%), leukocytes (3700/uL), platelet count (146000/ul) and neutrophils (66%) and lymphocyte (18%). The CRP level was improved into 5.7 mg/dL. On the 14th day of hospitalization, another chest X-ray was performed and there was an improvement compared to previous chest X-ray result. During treatment, the test results of PCR pharyngeal swab

of the patient showed two times positive results.

DISCUSSION

The patient came to emergency unit with a complaint of diarrhea since 3 days prior to hospital admission. She had liquid stool diarrhea for 3 to 4 times a day. She denied any symptom of fever during admission, but she said that she had cough once in a while without any shortness of breath. Chen et al in their epidemiological study and clinical characteristics of COVID disease suggested that 83% of patients came with fever, 82% had complained cough and only 2% of patients who came with a complaint of diarrhea.[6] Huang et al in their study in Wuhan also suggested that diarrhea was found only in 3% of the patients.[7] Fang et al.[8] found that diarrhea may occur starting from the 1st to 8th day of symptom onset with a median of 3.3 days. The mean duration may reach 4.1 (SD 2.5) days.[9] The patient came with a history of husband and sister had been tested positive for COVID-19; therefore, she was tested and observed in an isolation ward.

COVID-19 is a disease that can affect many organs and various kinds of appearance. In a case report, COVID-19 can affect the central nervous system such as stroke[10] and meningitis[11] Viral exanthem with "Pin and Needles Sensation" was also reported in one case report.[12] In the cardiovascular system, COVID-19 can cause several disorders such as arrhythmia to myocarditis.[13] Because of this, Pathak, in his editor's note said that COVID-19 can join several diseases that are called "The Great Imitator". But not only the Great Imitator, COVID-19 can also be called the Great Invader, because it not only attacks the respiratory system but also many other organs.[14]

Gastrointestinal symptoms in COVID-19 patients may include abdominal pain, nausea, vomiting and diarrhea. Guan et al.[15] in their study demonstrated that nausea and vomiting was found in 5% of the patients. In deceased patients, the gastrointestinal symptoms were more likely to be nausea and vomiting compared to living patients (6.9% vs 4.9%).[15] Xi Jin et al.[16] also reported that gastrointestinal symptoms are more frequently found in patients who got infected from their family compared to those who got the disease from other places. Similar exposure might occur in our patient as she probably got infected from her husband and sister who had been diagnosed with COVID-19 earlier. The risk for disease transmission through household cluster is supported by the possibility of oral-fecal transmission of COVID-19.[18] In tropical country during the transition of weather, diarrhea can be caused by various microorganisms including bacteria, virus and parasite; therefore, it is necessary to perform adequate history taking, physical examination and laboratory work up in order to establish the diagnosis. Therefore, during the time of COVID-19 pandemic, the early symptom of diarrhea calls for great caution for health care worker, particularly in establishing diagnosis.

Currently, it has been known that in addition to respiratory droplet and direct contact, COVID 19 may also be transmitted via oral-fecal route. Some case reports have demonstrated the presence of SARS-CoV-2 in saliva and stool of patients with COVID-19. It has been known that SARS-CoV-2 infection requires a contact with ACE2 receptor located on the type II alveolar cells, intestinal epithelium and cholangiocytes.[18] It has been suggest that intestinal ACE2 receptors associated with metabolism of amino acid, expression of antimicobial peptides and intestinal microbial balance.[19] In patients with COVID-19, diarrhea may also be caused through several mechanisms including direct viral infection of digestive tract that may result in mucosal damage and diarrhea. The mechanism is supported by the presence of protein of nucleocapsid virus on intestinal epithelial cells.[9] Although not yet known with certainty, but viral infections can cause increased permeability of the gastrointestinal mucosa, causing malabsorption.[20] Secondly, it may be caused by antiviral drugs and thirdly it may occur due to dysbiosis of intestinal microbiota which is induced by antibiotic usage.[9] In our patient, it may be caused by direct viral infection as the patient had diarrhea as initial symptom of COVID-19.

On hospital admission, radiological examination was performed showing results

of minimal infiltrate in the bottom left lung. Wong et al.[10] in their study demonstrated that the sensitivity of chest X-ray at initial phase was only about 69%; therefore, there were many positive cases had initially normal or uncharacterized chest X-ray. The aggravation of chest X-ray reached its peak on the 10th to 12th day after the onset of symptoms. The characteristic chest X-ray features for COVID-19 were peripheral infiltrate at the basal area and the involvement of both lungs. Pleural effusion was rarely found and it was only approximately 3% of the patients.[10] In our patients, there was infiltrate and aggravated results of chest X-ray examinations during her history of illness, which later improved. The initial laboratory workup found the following results of leukopenia (4300/uL), thrombocytopenia (132,000/uL), normal lymphocyte (30%) and CRP of 1.5; however, during the clinical history of illness, there was increased CRP, which was in line with exacerbated clinical symptoms.

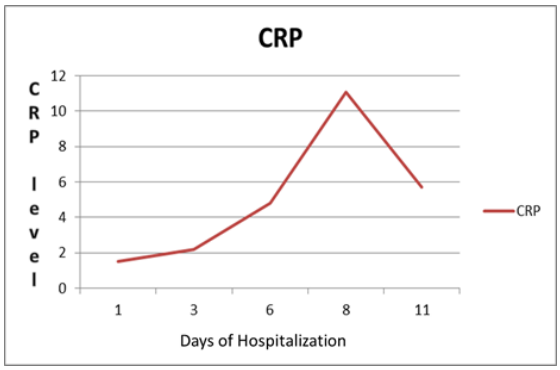


Figure 2. Graphic data on CRP level during hospitalization; CRP level, hospitalization day.

In the history of her present illness, the patient had another complaint of diarrhea on the 6th to 8th day of hospitalization and the complaint was followed by symptom of cough without any fever. Patients with COVID 19 in their history of illness may experience several phases starting from the prodromal phase, initial phase, pneumonia phase as well as inflammation and resolution. Pneumonia symptoms become more obvious in 4 to 7 days following the onset and inflammatory phase can be found in 8 to 12 days after the onset of disease.[21] Pneumonia and inflammatory phase are characterized by exacerbated clinical symptoms to Acute Lung Injury as well as increased level of acute phase protein such as CRP.[11,22] CRP is one of the laboratory tests that is recommended to be examined regularly in patients with COVID-19.[23] In our patient, there was increase CRP level, in which 1.5 mg/dL on the first day that increased to 2.2 mg/dL on the third day. Afterwards, it increased to 4.8 mg/dL on the 6th day and it reached the peak to 11.1 mg/dL on the eight day. Along with increased CRP level, the clinical respiratory symptoms became more obvious such as dry cough; however, it was not followed with fever. The symptoms were improved on the 10th to 11th day until the patient was discharged from hospital. The clinical improvement was observed through laboratory workup including improved chest X-ray results and improved CRP level to 5.7 mg/dL.

During hospital care, the patient received treatment of 500 mg chloroquine PO twice daily, 75 mg oseltamivir PO twice daily, 750 mg levofloxacin IV once daily, 400 mg vitamin C IV once daily, 5000 U of subcutaneous heparin twice daily as well as symptomatic treatment for cough and diarrhea. Chloroquine was given due to its ability in inhibiting viral entry and viral endocytosis as well as its capacity as an immunomodulator.[24] Chloroquine has gastrointestinal side effects such as nausea and vomiting, which probably had been experienced by our patient who had symptoms of nausea and loss of appetite. Guan et al suggested that increased D-dimer level was found in more than 40% of patients, which may be caused by microthrombus phenomenon.[25] Disrupted endothelial cell due to infection may result in the formation of thrombin causing hypercoagulability condition. Hypoxia may also occur in severe COVID-19 that may also induce thrombosis. (26) Tang et al in their study demonstrated that anticoagulant treatment may reduce mortality in patients with COVID-19.[26] Our patient had increased D-dimer from 600 ng/mL to 1900 ng/mL along with increased CRP and exacerbated clinical symptoms. Therefore, we decided to treat the patients with 5000 unit of heparin through subcutaneous injection twice daily. The patient was discharged from the hospital on the 14th

day of care without any complaint and she had improved laboratory and chest X-ray result. The patient then came for another follow-up visit in 1 week after her hospital discharge and she was in a good condition.

CONCLUSION

Coronavirus disease 2019 (COVID-19) is one of new infectious disease that emerges in December 2019. The clinical symptoms may be various, which requires great caution for health care worker in establishing diagnosis and providing treatment. Diarrhea, although it is rarely found, may become early and predominant manifestation of COVID-19; therefore, a thorough directed history taking and appropriate examination are necessary for diagnosis.

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REFERENCES

1. Coronavirus disease (COVID-2019) situation reports [Internet]. WHO. 2020 [cited 2020 May 7]. Available from: Coronavirus disease (COVID-2019) situation reports.
2. Gugus Tugas Percepatan penanganan COVID19. Data Sebaran Covid Indonesia [Internet]. 2020 [cited 2020 May 7]. Available from: https://covid19.go.id/
3. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929–36.
4. Ata F, Almasri H, Sajid J, Yousaf Z. COVID-19 presenting with diarrhoea and hyponatraemia. BMJ Case Rep. 2020;13(6):1–3.
5. Song Y, Liu P, Shi XL, et al. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut. 2020:1143–4.
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
8. Fang D, Ma J, Guan J, et al. Manifestations of Digestive system in hospitalized patients with novel coronavirus pneumonia in Wuhan, China: a single-center, descriptive study. Chin J Dig. 2020;40.
9. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Alimentary Pharmacology and Therapeutics. 2020:843–51.
10. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. Brain, Behav Immun. 2020;87(January):115–9.
11. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis [Internet]. International Society for Infectious Diseases. 2020;94(March):55–8. Available from: https://doi.org/10.1016/j.ijid.2020.03.062
12. Putra BE, Adiarto S, Dewayanti SR, Juzar DA. Viral exanthem with "Spins and needles sensation" on extremities of a COVID-19 patient: A self-reported case from an Indonesian medical frontliner. Int J Infect Dis [Internet]. 2020;96:355–8. Available from: https://doi.org/10.1016/j.ijid.2020.05.020.
13. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response [Internet]. Current Problems in Cardiology. 2020:1–9. Available from: http://dx.doi.org/10.1016/j.biochi.2015.03.025 http://dx.doi.org/10.1038/nature10402 http://dx.doi.org/10.1038/nature21059 http://journal.stainkudus.ac.id/index.php/equilibrium/article/view/1268/1127 http://dx.doi.org/10.1038/nrmicro2577 http://
14. Pathak N. The great invader: How COVID-19 attacks every organ [Internet]. medscape. 2020 [cited 2020 Jul 8]. Available from: https://www.medscape.com/viewarticle/929284
15. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020.
16. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;1002–9.
17. Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet [Internet]. Elsevier Ltd; 2020;395(10223):514–23. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30154-9.
18. Abbas Z, Zaheer R. Clinical insight into the involvement of gut and liver by COVID-19. 2019;2019:2019–20.
19. Hashimoto T, Perlot T, Rehman A, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. Nature Publishing

Group; 2012;487(7408):477–81.
20. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology [Internet]. 2020;158(6):1518–9. Available from: https://doi.org/10.1053/j.gastro.2020.02.054.
21. Susilo A, Rumende CM, Pitoyo CW, et al. Coronavirus disease 2019: Tinjauan literatur terkini Coronavirus disease 2019: Review of current literatures. J Penyakit Dalam Indones. 2020;7(1):45–67.
22. Mahrous AA, Hassanien AA, Atta MS. Predictive value of C-reactive protein in critically ill patients who develop acute lung injury. Egypt J Chest Dis Tuberc [Internet]. 2015;64(1):225–36. Available from: http://dx.doi.org/10.1016/j.ejcdt.2014.10.006.
23. Burhan E, Susanto AD, Nasution S, et al. Protokol tatalaksana COVID-19. Jakarta: PDPI-PERKI-PAPDI-PERDATIN-IDAI; 2020.
24. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for Coronavirus disease 2019 (COVID-19): A review. JAMA. 2020;2019.
25. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020;1–13.
26. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020:1094–9.

Prevention of Ventricular Arrhythmia and Sudden Cardiac Death in COVID-19 Patients

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ABSTRAK

Sejak kasus pertama dilaporkan pada akhir 2019, COVID-19 telah menyebar ke seluruh dunia dan menjadi pandemi. Tingginya tingkat penularan virus, menjadi ancaman bagi kesehatan masyarakat secara global. Infeksi virus dapat memicu sindrom koroner akut, aritmia, dan timbulnya eksaserbasi gagal jantung. Hal ini terutama diakibatkan kombinasi respon inflamasi sistemik yang signifikan disertai inflamasi vaskular terlokalisir pada plak arteri, bersama dengan efek lainnya. Panduan praktik klinis di Indonesia untuk tata laksana COVID-19 menyebutkan bahwa hydroxychloroquine sendiri atau kombinasi dengan azithromycin berpotensi digunakan untuk terapi COVID-19. Namun, chloroquine, hydroxychloroquine, dan azithromycin dapat memperpanjang interval QT. Hal ini meningkatkan kekhawatiran tentang risiko kematian akibat aritmia dari penggunaan obat ini secara individu atau kombinasi. Sampai saat ini masih belum ada vaksin dan antivirus spesifik untuk terapi COVID-19, sehingga pencegahan untuk pada pasien dengan risiko kardiovaskular dan efek samping pengobatan sangat diperlukan.

Kata kunci: *COVID-19, aritmia, hydroxychloroquine, azithromycin, pemanjangan interval QT.*

ABSTRACT

Since the first case was reported at the end of 2019, COVID-19 has spread throughout the world and has become a pandemic. The high transmission rate of the virus has made it a threat to public health globally. Viral infections may trigger acute coronary syndromes, arrhythmias, and exacerbation of heart failure, due to a combination of effects including significant systemic inflammatory responses and localized vascular inflammation at the arterial plaque level. Indonesian clinical practice guideline stated that (hydroxy)chloroquine alone or in combination with azithromycin may be used to treat for COVID-19. However, chloroquine, hydroxychloroquine, and azithromycin all prolong the QT interval, raising concerns about the risk of arrhythmic death from individual or concurrent use of these medications. To date, there is still no vaccine or specific antiviral treatment for COVID-19. Therefore, prevention of infection in people with cardiovascular risk and mitigation of the adverse effects of treatment is necessary.

Keywords: *COVID-19, arrhythmia, hydroxychloroquine, azithromycin, prolong QT interval.*

INTRODUCTION

COVID-19 has reached a pandemic level and is a threat to global health. Its course is still evolving. Lessons from the previous coronavirus and influenza epidemics suggest that viral infections can trigger acute coronary syndromes, arrhythmias, and exacerbation of heart failure, due to a combination of effects including significant systemic inflammatory responses and localized vascular inflammation at the arterial plaque level.[1]

Patients with pre-existing cardiovascular disease may have a worse prognosis than others, although age could be one of the confounders. Furthermore, although most clinical presentations involve the respiratory system, the disease may also impact on the cardiovascular system. Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV2, the causative virus of COVID-19. Besides its expression in the respiratory system, ACE2 is found in the human cardiovascular system including the heart. Infection by SARS-CoV2 can cause damage to the myocardium, although the specific mechanisms are uncertain.[2]

Pro-arrhythmic effects of COVID-19-related issues include fever, stress, electrolyte disturbances, and pharmacological treatment. These may impact patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions, as comorbidities, or consequent to inherited syndromes. The safety of QT-prolonging medications may be maximized by close monitoring and optimization of these factors.[1,2]

LONG QT SYNDROME

A registry of 1099 cases with COVID-19 reported a higher prevalence of hypertension and coronary artery disease in severely affected versus non-severely affected patients. Another study compared patients admitted to the intensive care unit (ICU) and on-ICU patients. Higher rates of hypertension and cardiovascular diseases were observed in ICU patients.[3,4]

COVID-19 may have an arrhythmogenic effect, potentially contributing to disease outcome—this could be of importance for patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions, comorbidities, or consequent to inherited syndromes. Inherited arrhythmia syndromes such as long QT syndrome (LQTS), Brugada syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (VT) in the setting of the COVID-19 pandemic may prove particularly challenging. These patients may be susceptible to the pro-arrhythmic effects of COVID-19-related issues such as fever, stress, electrolyte disturbances, and the use of antiviral drugs. Hence, additional precautions and preventive measures are recommended, including electrocardiogram (ECG) monitoring, aggressive antipyretic treatment, and more stringent social distancing to prevent infection.[5,6]

LQTS is characterized by abnormally prolonged ventricular repolarization and an increased risk of the malignant arrhythmia torsades de pointes and ventricular fibrillation that may lead to sudden death. The greatest risk factor for malignant arrhythmias in patients with LQTS or acquired QT prolongation is the use of one or more corrected QT interval (QTc)-prolonging drugs in the setting of severe manifestation of COVID 19.6 COVID-19 treatment with a combination of (hydroxy) chloroquine and additional antivirals, or with azithromycin, may result in higher plasma levels and significant QT prolongation. Physicians should also be aware of the alpha-blocking effects of (hydroxy)chloroquine, which might result in hypotension.[6]

The patient's baseline QTc value should be obtained before administering any drugs with the potential to prolong the QT interval. There still no guidance regarding how to monitor outpatients that use (hydroxy)chloroquine. Ambulatory ECG monitoring may be considered. It is also important for patients being treated with QT-prolonging drugs to report promptly any new symptoms including palpitation, syncope, or near syncope. They should also report clinical changes that could lead to hypokalemia, such as gastroenteritis or the initiation of diuretic therapy.[6,7]

In general, patients with the following QTc intervals are at low risk for significant QT prolongation and polymorphic VT:

- QTc < 460 ms in pubertal males/females
- QTc < 470 ms in postpubertal males
- QTc < 480 ms in postpubertal females.

PREVENTION OF ARRHYTHMIA AND SUDDEN CARDIAC DEATH IN LQTS PATIENTS

Patients with the baseline QTc interval ≥500 ms (with a QRS ≤ 120 ms) are at increased risk for significant QT prolongation and polymorphic VT.[8] In such patients, efforts should be made to correct any contributing electrolyte abnormalities: for hypokalemia correct to a level of > 4 mEq/l and for hypomagnesemia correct to a level of >2 mg/dl. Withhold the drugs in patients with baseline QT interval prolongation (QTc 500 ms) or with known congenital LQTS.[7] Patients with a risk of QT prolongation or history of LQTS that are hospitalized with COVID-19 infection need monitoring, dose adjustment, and possibly drug discontinuation.[7]

Patients must be monitored and serum potassium optimized daily. An ECG should be acquired 2-3 h after the second dose of (hydroxy)chloroquine, and daily thereafter. If QTc increases by > 60 ms and/or absolute QTc > 500 ms (or > 530–550 ms if QRS > 120 ms), azithromycin should be discontinued and/or the dose of (hydroxy)chloroquine should be reduced, and the ECG should be repeated daily. If the QTc remains increased, the risk and benefit of ongoing therapy should be re-evaluated, consultation with an electrophysiologist should be considered, and discontinuation of (hydroxy) chloroquine should also be considered.There should be a reevaluation of the risk of torsades de pointes versus benefit of the medication, with the considerations as follows:[8]

- Recognition that there is an increased risk of torsades de pointes,
- Discontinuation of all other QT-prolonging medications,
- Correction of all electrolyte abnormalities,
- Placement of the patient in continuous telemetry, with consideration of a wearable defibrillator or placement of external defibrillator patches,
- Discontinuation of (hydroxy)chloroquine, azithromycin, or other medication if torsades de pointes develops.

The safety of QT-prolonging medications may be maximized by close monitoring and optimization of these factors. A risk score has been derived and validated by Tisdale et al., for prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients (**Table 1** and **2**).[9]

Table 1. Risk score for drug-associated QTc prolongation

Risk Factors	Points
Age ≥ 68y	1
Female sex	1
Loop diuretic	1
Serum K+ ≤ 3.5 mEq/l	2
Admission QTc ≥ 450 ms	2
Acute MI	2
≥ 2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum risk score	21

QTc, corrected QT interval; MI, myocardial infark. Risk scores as derived and validated by Tisdale et al.[9]

Table 2. Risk levels for drug-associated QT prolongation

Risk Levels	Points
Low Risk	≤ 6
Moderate Risk	7–10
High Risk	≥ 11

This scoring can help clinicians to monitor COVID-19 patients given (hydroxy)chloroquine and azithromycin so that mortality and morbidity caused by these combinations can be reduced. However, there are still no data showing that this scoring can help prevent drug-associated torsades de pointes.[9]

Patients admitted with COVID-19 are likely to have longer baseline QTc and have higher potential arrhythmic risks as a result of the metabolic and physiologic sequelae of their illness, and typically a greater burden of comorbid disease. The goal of QTc screening in this setting is not to identify patients who

are not candidates for therapy but to identify those who are at increased risk for torsades de pointes, so aggressive countermeasures may be implemented.8 The QTc calculation for screening can use several formulas, which are summarized in **Table 3**.

Table 3. QTc formulas.

QTc formulas	Equation
Fridericia	QTc = QT/ $\sqrt[3]{RR}$
Framingham	QTc = QT + 0.154(1-RR)
Hodges	QTc = QT 1.75(HR-60)
Bazett	QTc = QT/ $\sqrt[2]{RR}$

Fridericia or Framingham correction should be considered especially for heart rates > 90 bpm[10]

Patients who are stable for outpatient therapy may be less at risk for complications, but are unlikely to have access to close monitoring. If ECG assessment of an outpatient is impossible or poses an undue risk of infection for others, the necessity of treatment should be balanced against risk when considering alternative monitoring methods or omitting monitoring. If quarantine or resource constraints are prohibitive, consider performing no further ECG/telemetry assessment if the Tisdale risk score ≤ 6. Otherwise, ECG should be repeated 2-3 h after dosing on day 3 of therapy. If QTc increases by > 30–60 ms or absolute QTc > 500 ms (or > 530–550 ms if QRS > 120 ms), discontinuing therapy should be considered.[7,8] The drug administration flowchart based on QT is shown in **Figure 1**.

BRUGADA SYNDROME

Brugada syndrome is a familial arrhythmia syndrome disorder characterized by the type 1 Brugada ECG pattern in the right precordial leads of the ECG and an increased risk for ventricular fibrillation and sudden cardiac death. The most frequently-used drugs for COVID-19 patients are not on the list of drugs to be avoided by Brugada syndrome patients.[6,11]

However, attention to Brugada syndrome

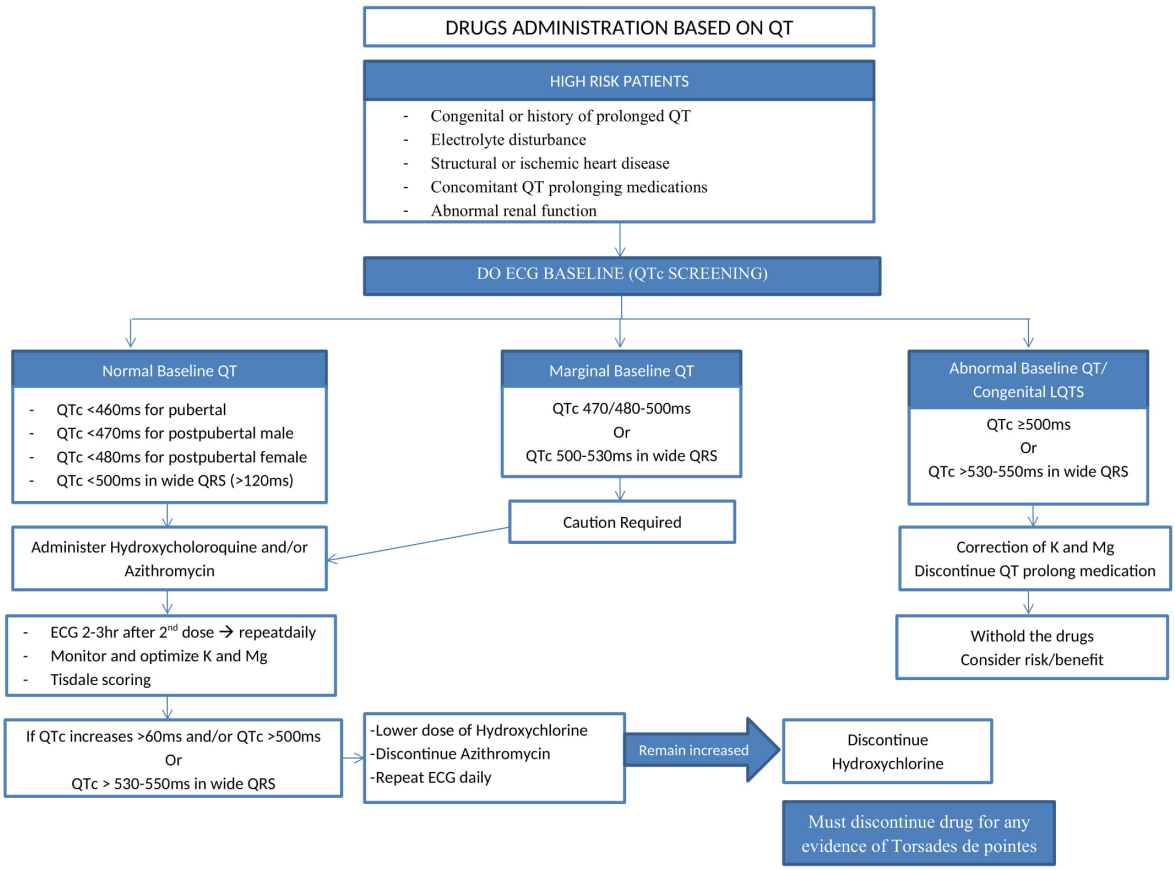

Figure 1. The drug administration flowchart based on QT.

management is relevant in the setting of the COVID-19 outbreak since ECG manifestations of the disorder may be uncovered during fever, and since fever has been unequivocally associated with life-threatening arrhythmic events in patients with the disorder.[12] Individuals with Brugada syndrome may be at increased risk for ventricular arrhythmias during fever. Fever may aggravate the coved-type ST-segment elevation in leads V1 and V2 that often precedes arrhythmias in Brugada syndrome.[13]

PREVENTION OF ARRHYTHMIA AND SUDDEN CARDIAC DEATH IN BRUGADA SYNDROME PATIENTS

Based on the aboves statement, the following recommendations are:[6]

- All patients with Brugada syndrome should self-treat with paracetamol or acetaminophen immediately if they develop signs of fever, and self-isolate.
- Patients without an implantable cardioverter defibrillator (ICD) who are at higher risk due to fever include:
  a. Sodium channel disease with or without type 1 ECG pattern
  b. Children and young adults (< 26 years old) and the elderly (> 70 years) with Brugada syndrome
  c. All patients with a spontaneous type 1 Brugada pattern and/or cardiac syncope.
- If these higher-risk patients develop a high fever (> 38.5 oC) despite paracetamol treatment, they will need to attend the emergency department. Assessment should include an ECG and monitoring for arrhythmia. If an ECG shows the type 1 Brugada ECG pattern, then the patient will need to be observed until fever and/or the ECG pattern resolves. If all ECG show no sign of the type 1 ECG pattern, then they can go home to self-isolate.
- Patients who are not part of the higher-risk group and have a drug-induced type 1 ECG pattern, no symptoms of syncope, and no sign of a spontaneous type 1 pattern at any other time are at the lowest risk and can afford to self-isolate at home.

Malignant arrhythmia in the setting of elevated cardiac markers should raise suspicion of underlying myocarditis.

Although hypoxia and electrolyte abnormalities that are common in the acute phase of severe illness can potentiate cardiac arrhythmias, the exact arrhythmic risk due to COVID-19 in patients with less severe illness or those who recover from the acute phase of the severe illness is currently unknown.[14] Improved understanding of this is critical, primarily in guiding decisions on whether additional arrhythmia monitoring is needed (e.g., mobile cardiac telemetry) after discharge and whether an ICD or wearable cardioverter defibrillator will be needed in those with impaired left ventricular function thought to be secondary to COVID-19.[14]

PROTOCOL MODIFICATIONS IN SETTINGS WITH LIMITED RESOURCES OR QUARANTINE

In settings where resource limitation or quarantines preclude the full implementation of the above guidelines, the following modifications should be used:[8]

- To minimize exposure or contact, it may be reasonable to forego ECG screening to allow patients to remain in quarantine if no high-risk features exist (history of LQTS, concomitant QT-prolonging medications, structural or ischemic heart disease, history of prolonged QTc on any ECG, history of abnormal renal function and/or electrolytes).
- All patients should have close monitoring of symptoms with attention to indicators of arrhythmia risk (syncope, dehydration, initiation of new medications, and worsening of health status).
- If telemetry resources are limited, their use must be triaged based on clinical importance. Patients already on therapy with QTc values in the acceptable range could be considered for ongoing (hydroxy)chloroquine use without telemetry. Patients initiating therapy with Tisdale risk score ≤ 6 can similarly be considered for use without monitoring. Any syncope should be considered due to polymorphic VT and should prompt to ECG and re-initiation of telemetry.

GENERAL PREVENTION

Electrocardiography

All patients in whom COVID-19 is suspected should have a baseline electrocardiogram performed at the time of entry into the health care system. Ideally, this would be a 12-lead ECG. This will allow for documenting baseline QRS-T morphology should the patient develop signs or symptoms suggestive of myocardial injury or an acute coronary syndrome. Additionally, the baseline ECG allows for documentation of the QT (and QTc) interval. Importantly, QTc will need to be monitored if QT-prolonging therapies are initiated (eg; azithromycin and chloroquine) to reduce LQTS.[15]

Cardiac Markers

The mortality rate has been reported to be higher in patients who had COVID-19 with high troponin T (TnT) levels than those with normal TnT levels. Patients with high TnT levels have demonstrated elevated levels of N-terminal pro B-type natriuretic peptide (NT ProBNP). Elevated NT ProBNP is related to malignant arrhythmia.[16]

Public Health

Clinic visits and in-person cardiac implantable electronic device checks should be changed to telehealth and remote checks whenever feasible.[14] At a population level, large-scale public health interventions with preparedness plans and mitigation interventions are being developed and implemented. Public health measures include self-isolation and quarantining the infected patients as well as early detection of the disease. Aggressive compliance with basic hygiene skills along with minimizing the exposure to COVID-19 is key to preventing the spread of COVID-19 and should be strongly implemented.[1]

During this pandemic, patients should avoid close contact with other patients with suspected or confirmed COVID-19 or having signs and symptoms of respiratory infection. Hand washing and social distancing are the key principles to reduce the risk of infection. Patients with underlying cardiac disease, hypertension, cardiac transplant patients, or patient taking immunosuppressive medications should take extra precautions to avoid becoming infected.[1]

CONCLUSION

Patients with pre-existing cardiovascular disease may have a worse prognosis than others, although age could be a confounding factor. These patients may be susceptible to pro-arrhythmic effects of COVID-19-related issues such as fever, stress, electrolyte disturbances and pharmacological treatment.

Treatment with (hydroxy)chloroquine and additional drugs, or with azithromycin, might result in higher plasma levels and significant QT prolongation, necessitating additional precautions and specialized management. Key precautions include hand washing and social distancing to reduce the risk of infection, aggressive antipyretic treatment to reduce fever in Brugada syndrome patients, and ECG monitoring and scoring in LQTS patients treated with antiviral drugs. Recognition of cardiovascular or arrhythmia risk in COVID-19 patients is necessary.

ACKNOWLEDGMENTS

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REFERENCES

1. Madjid M, Safavi-Naeini P, Solomon SD, et al. Potential effects of Coronaviruses on the cardiovascular system: A review. JAMA Cardiol. 2020;10:1–10.
2. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol [Internet]. 2020;17(5):259–60. Available from: http://dx.doi.org/10.1038/s41569-020-0360-5.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9.
4. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.
5. Weiss P, Murdoch DR. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- company' s public news and information website . Elsevier hereby grants permission to make all its COVID-19-r. 2020.

6. Wu C-I, Postema PG, Arbelo E, et al. SARS-CoV-2, COVID-19, and inherited arrhythmia syndromes. Heart Rhythm. 2020.
7. Roden DM, Harrington RA, Poppas A, et al. Considerations for drug interactions on QTc interval in exploratory COVID-19 treatment. J Am Coll Cardiol. 2020;75(20):2623–4.
8. Ventricular arrhythmia risk due to Hydroxychloroquine-Azithromycin treatment for COVID-19 - American College of Cardiology [Internet]. [cited 2020 Jun 12]. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19.
9. Tisdale JE, Jaynes HA, Kingery JR, et al. Interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2014;1–21.
10. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? J Am Heart Assoc. 2016;5(6).
11. Postema PG, Neville J, De Jong JSSG, et al. Safe drug use in long QT syndrome and Brugada syndrom. Europace. 2013;15(7):1042–9.
12. Casado-arroyo R, Leshem E, Juang JJM. Fever-related arrhythmic events in the multicenter survey on arrhythmic events in Brugada syndrome (SABRUS) brief title: Brugada syndrome and fever-related arrhythmias. (9):1–21.
13. Amin AS, Klemens CA, Verkerk AO, et al. Fever-triggered ventricular arrhythmias in Brugada syndrome and type 2 long-QT syndrome. Netherlands Hear J. 2010;18(3):165–9.
14. Kuck KH. Arrhythmias and sudden cardiac death in the COVID-19 pandemic. Herz. 2020;3–4.
15. Cheung CC, Davies B, Gibbs K, et al. Multi-lead QT screening is necessary for QT measurement: Implications for management of patients in the COVID-19 era. JACC Clin Electrophysiol. 2020.
16. Gao L, Jiang D, Wen XS, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res. 2020;21(1).

Discordance Between Clinical Status and Chest X-Ray (CXR) in COVID-19 Patient with Asymptomatic Transmission in Jakarta

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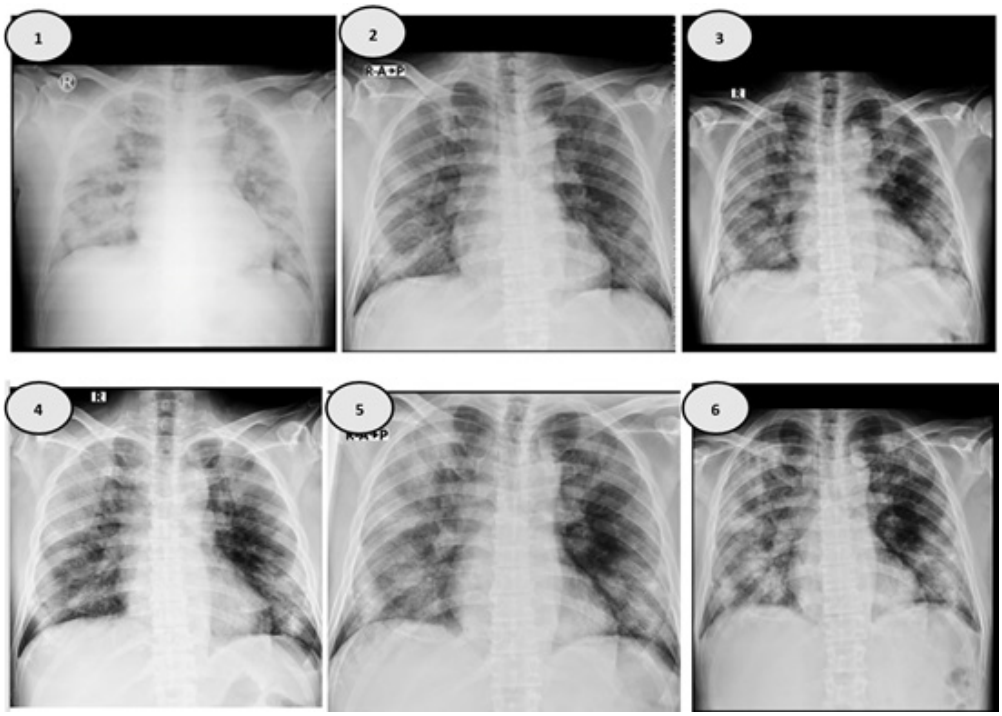

Figure 1. Series of CXRs starting from day 1 up to 7 of hospitalization. CXRs at day 1 (1), day 3 (2), day 4 (3), day 5 (4), day 6 (5), and at day 7 of hospitalization (6), each. According to the CXRs, the patient's pneumonia and infiltration improved.

Coronavirus Disease 2019 (COVID-19) symptoms are highly various in each patient. Patients with COVID-19 may show severe symptoms with severe pneumonia and ARDS, mild symptoms resembling simple upper respiration tract infection, or even completely asymptomatic.[1] Few are known about the natural progression of COVID-19 and whether its pneumonia follow the pattern of pneumonia caused by other microorganism. Chest X-ray (CXR) is an affordable and simple radiology modality routinely used to monitor patient with

COVID-19. It is not known whether CXR is useful for monitoring COVID-19 patient.

Male, 55 years-old, Mr. F, experienced symptoms of respiratory disease. On the first day of symptoms, the patient developed fever of 38 ^{o}C, gradually followed by dry cough and sore throat. On day 7 of symptoms, patient experienced mild dyspnea. The patient underwent CXR leading to the diagnosis of severe pneumonia. Hence, the patient was admitted to emergency room at department of pulmonology of the Persahabatan Hospital, Jakarta, on day 8 of symptoms (day 1 of hospitalization).

The patient had no history of contact with confirmed or presumed COVID-19 patients, nor any known travel history. Patient's wife had close contact to confirmed COVID-19 patients. The wife was reported to be healthy with no symptoms. However, she refused to be tested for COVID-19.

During 8 days of hospitalization, the patient received CXR daily. (**Figure 1**) There was a gradual improvement of lung lesion seen on CXR starting from the first day of hospitalization. However, patient clinically deteriorate and suffered from severe dyspnea on the fourth day of hospitalization.

The patient required oxygen therapy delivered through high flow nasal canule and Optiflow. In addition, the patient was treated with Oseltamivir 2 x 75 mg, chloroquin 2 x 500 mg, Levofloxacin 1 x 750 mg, Vitamin C 2 x 1000 mg, Vitamin B1 1 x 100 mg, Vitamin B6 1 x 100 mg, and Vitamin B12 1 x 200 mcg. The patient was discharged after 15 days of hospitalization following two negative RT-PCR COVID-19 tests.

It is important to note that COVID-19 symptoms are highly variable. Patients may show severe or mild symptoms, or just be asymptomatic.[2] Ye, et al.[2] reported about case series including a familial cluster with asymptomatic transmission. In our study, patient never had contact with COVID-19 patient. In this case, wife might acted as asymptomatic carrier for our patient.

CXR finding in this patient does not correlate well with improvement of clinical condition. On the day 8 of symptoms (day 1 of hospitalization), CXR showed a wide bilateral infiltrate. However, patient only experienced mild dyspnea. CXR was conducted on the first day of hospitalization and started improving on day 2 and the following day. However, the patient continued to clinically deteriorate as well as developed severe dyspnea requiring higher level of oxygen therapy on day 4 of hospitalization. This discordance between CXR finding and clinical status may be caused by cytokine storm leading to acute respiratory distress syndrome (ARDS).[3] It may also caused by fibrosis formation that develop at the late stage of COVID-19 infection.[4]

Asymptomatic transmission is possible in COVID-19. Clinician attending COVID-19 patient must rely on monitoring the clinical presentation of the patient and not solely on CXR improvement.

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REFERENCES

1. Q&A on coronaviruses (COVID-19) [Internet]. [cited 2020 Apr 3]. Available from: https://www.who.int/news-room/q-a-detail/q-a-coronaviruses.
2. Ye F, Xu S, Rong Z, et al. Delivery of infection from asymptomatic carriers of COVID-19 in a familial cluster. Int J Infect Dis. 2020 May;94:133–8.
3. Xie P, Ma W, Tang H, Liu D. Severe COVID-19: A review of recent progress with a look toward the future. Front Public Health. 2020;8:189.
4. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol. 2020;19:1–9.

COVID-19 Pandemic in Indonesia: Situation and Challenges of Rehabilitation Medicine in Indonesia

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ABSTRAK

COVID-19 telah menjadi pandemik di Indonesia sejak ditemukannya kasus pertama pada tanggal 2 Maret 2020 di Depok. Peningkatan kasus perhari semakin tinggi sejak akhir Agustus 2020 yang mencapai lebih dari 2000 kasus per hari. Sistem kesehatan di Indonesia perlu ditingkatkan dalam hal kapasitas, termasuk rehabilitasi medik yang harus dilibatkan dari fase akut hingga jangka panjang dalam penanganan pasien COVID-19. Rehabilitasi medik juga diperlukan untuk pasien lain yang bukan COVID-19. Pentingnya keterlibatan, pelayanan rehabilitasi medik dan implementasinya dimasa pandemic COVID-19 memerlukan strategi tersendiri yang harus dilakukan baik oleh pekerja kesehatannya, rumah sakit dan kebijakan pemerintah. Hal ini diperlukan untuk percepatan peningkatan kesehatan pasien, percepatan pemulangan dan menghindari readmisi pasien, dan juga pengoptimalan program kembali bekerja untuk pasien yang sembuh dari COVID-19.

Kata kunci: *COVID-19, rehabilitation, health care, rehabilitation services, pandemic.*

ABSTRACT

COVID-19 has become a pandemic in Indonesia since the first cases have been positively diagnosed on 2 March 2020 in Depok. The cases have been increased gradually since the end of August 2020 that has reached 1000 cases per day. The health system in Indonesia needs to be improved in terms of capacity, including rehabilitation medicine that should be involved in all health phases (from acute to long-term) in managing patients with COVID-19. Rehabilitation is also still needed for other non-COVID-19 patients. The importance of involvement and implementation of rehabilitation services during the COVID-19 pandemic will need special strategies that should be done by rehabilitation professionals, hospitals, and government. These are necessary to accelerate the improvement of patients' health, discharge, and avoid re-admission, as well as optimize return-to-work for patients who are recovered from COVID-19.

Keywords: *COVID-19, rehabilitation, health care, rehabilitation services, pandemic.*

INTRODUCTION

The COVID-19 pandemic that has started in Wuhan, China, has been spread all over the world since the end of 2019.[1] Covid-19 can infect all individuals of all ages,[2-4] and people at all levels of economic status.[3] However, persons with a high risk of severe or fatal course of the disease are older individuals and people with comorbidity, such asdiabetes, cancer, and other chronic diseases.[5-7]

In Indonesia, the first cases of COVID-19 patients were identified on 2 March 2020 in Depok. Since the ends of August 2020, the number of new positively tested cases in Indonesia have reached more than two thousand per day (**Figure 1**). Currently (as of 8 September 2020), the total number of positively diagnosed cases reached more than 196,000.[8]

The confirmed cases of COVID-19 in Indonesia are placed the second among Association of South-East Asia Nations (ASEAN) countries (**Table 1**). However, the numbers of deaths are the highest. Both numbers of positive and death cases will keep increasing, considering the current total tested per Million populations in Indonesia are still low as compared to other countries. It seems that Indonesia will still need time to flatten the curve. Although the recovered cases are the highest among ASEAN countries, it does not mean that all recovered patients are without any lingering effects, such as fatigue, dyspnea, joint pain, chest pain, headache, muscle weakness, neurological symptoms, and mental health problems.[9] Therefore, the recovered patients still need treatments, which mostly related to rehabilitation.

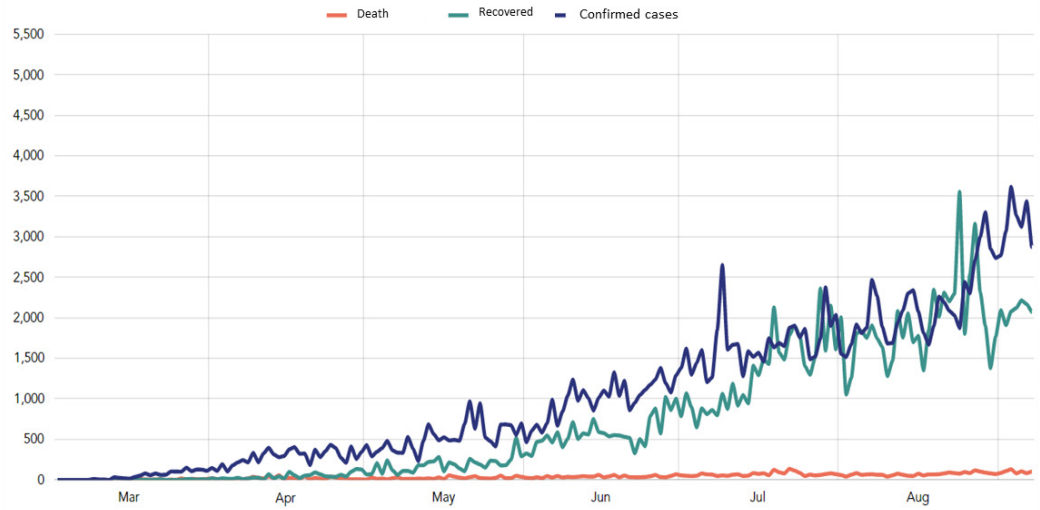

Figure 1. Data of COVID-19 in Indonesia.[8]

Table 1. Covid-19 cases in ASEAN countries (as of 7 September 2020).[10]

Countries	Confirmed cases	Total deaths	Total recovered	Test/1M Population	Total population
Philipines	238,727	3,890	184,906	25,855	109,850,251
Indonesia	196,989	8,130	140,652	8,948	274,061,093
Singapore	57,044	27	56,408	353,013	5,858,949
Malaysia	9,459	128	9,124	40,300	32,422,628
Thailand	3,445	58	3,281	10,729	69,833,165
Vietnam	1,049	35	853	10,350	97,501,966
Myanmar	1,518	8	388	3,055	54,478,228
Cambodia	274	--	272	6,356	16,761,610
Brunei	145	3	139	121,013	438,259
Laos	22	--	21	5,714	7,294,985

Similar to other countries all over the world, the government of Indonesia has been awaiting the development of effective medicine and vaccines. From the perspective of public health issues, many issues need to be taken promptly and accurately. During this period, some important actions have been also implemented by the government of Indonesia in order to reduce, control and mitigate the spread of SARS-CoV-2 infection, particularly by following actions: (1) Physical distancing, hand washing, cough and sneeze etiquette, as well as isolation; (2) Massive detection/testing for COVID-19 (both by swab test and/or rapid test) and tracing; (3) Increasing capacity of hospitals, particularly hospitals that are appointed as referral hospitals for COVID-19 patients; (4) Establishing national COVID-19 emergency team.

According to the survey that was held by the World Health Organization (WHO), the COVID-19 pandemic has influenced the health services worldwide, particularly in the low-and middle-income countries.[10] In spite of rehabilitation play a major role in recovery after a severe illness due to COVID-19, the most effected health service is rehabilitation.[11] It was effected rehabilitation services in 63% out of 153 countries that were surveyed, particularly in low-and low-middle income countries.[11] Therefore, WHO has urged their member states that rehabilitation should be integrated into the national strategy for managing the COVID-19 pandemic.[11]

Considering the importance and relevancies of rehabilitation medicine during COVID-19, several important and relevant points need to be highlighted and discussed for Indonesia. These include: (a) What are the rehabilitation needs for COVID-19 patients; (b) The effects of reducing the capacity of rehabilitation services for other patients (non-COVID-19) in need for rehabilitation (e.g. people with disability, patient with chronic diseases (e.g. cancer, traumatic brain injury, spinal cord injury, stroke, diabetes, chronic pain, etc); (c) Situation and challenges of rehabilitation medicine in long-term COVID-19 pandemic in Indonesia.

REHABILITATION NEEDS FOR COVID-19 PATIENTS

It has been known that the primary problem of patients with COVID-19 is respiratory functions. This was particularly due to the cytokine storm[12,13] that leads to acute respiratory distress syndrome. The symptoms in moderate and severe problem patients, particularly related to the respiratory impairments (e.g. difficult to breathe). However, many findings have reported also non-pulmonary manifestations and complications problems.[14] These include

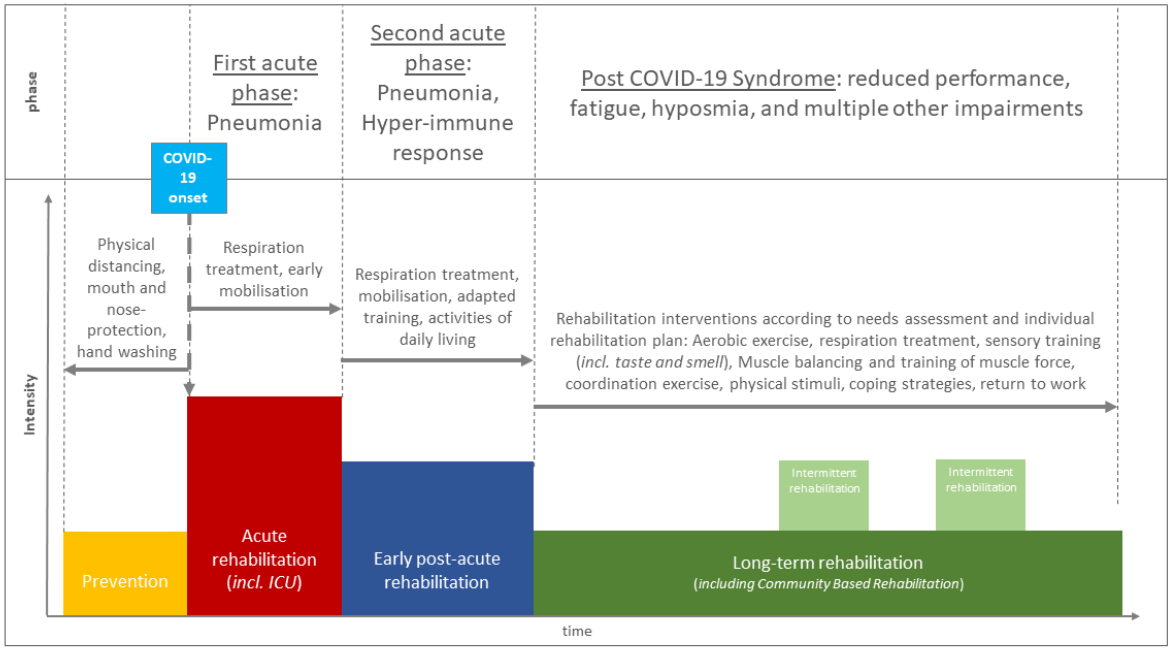

Figure 2. Phase-specific rehabilitation response for patients with SRAS-CoV-2 infection.

muscle weakness, delirium, swallow and communication problems, neurological and psychiatric sequelae.[15] Therefore, patients with moderate and severe cases of COVID-19 have a high need for rehabilitation interventions.[16] Additionally, rehabilitation for COVID-19 patients should be implemented in all phases (acute to long-term phases).[16] This also can be seen in **Figure 2**.

COVID-19 is still not yet fully understood, however, many studies related to the mechanisms of this disease (many of them are observational) have been published. It becomes more and more evident, that the disease is not only an airway infection but also causes a hyper-immune response in the body.[12,17-19] This may explain the broad spectrum of long-term organ dysfunction and functional symptoms.[20,21] Many of the symptoms and dysfunctions can be treated by rehabilitation interventions. As clinical outcome studies have not yet been performed, the approach at this stage is pragmatic and symptom-oriented. The main symptoms observed frequently are summarized in **Table 2**, and pragmatic rehabilitation approaches are listed (for more details see literature and

Table 2. Overview of clinical/organ impairment due to SARS-CoV-2 infections, rehabilitation needs, and interventions.

Organ system and functioning problems	Symptoms with rehabilitation needs	Rehabilitation interventions			
		Hospitalized patients		Discharged patients	
		Acute care (including critical care)	Early-post acute care	Post-acute rehabilitation	Long-term rehabilitation
Respiratory system	Respiratory insufficiency, low oxygen uptake	Breathing exercise, positioning	Breathing exercise, assistive respiration treatment, early mobilization	Breathing exercise, aerobic exercise, nutritional support	
Central and peripheral nervous system	Headache, dizziness, confusion, pain, consciousness, delirium, cognitive dysfunction	Passive and assisted movements, sensory stimulation, early mobilization	Assisted and active movements, neurophysiological techniques, sensory stimulation, cognitive training	Coordinative training, gait training, training of activities of daily living, cognitive training (incl. telerehabilitation)	
	Stroke				
	Sensory dysfunction, i.e. smell and taste dysfunction	Smell training		Smell training	
	Dysphagia, communication problems	Dysphagia management, speech therapy		Dysphagia management, speech therapy (incl. telerehabilitation)	
	Paresthesia, dyscoordination	Coordination exercise, sensory stimuli		Coordination exercise, sensory stimuli	
Musculoskeletal system	Muscle weakness an muscular imbalance, muscle pan	Passive an assisted movements, muscle balancing, early mobilization	Assisted and active mobilization and positioning, adapted muscle exercise	Aerobic training, muscle strengthening exercise, balancing muscle tone	
Cardiovascular system	Myopericarditis, hypoxia, heart failure	Graded early mobilization, peripheral vascular training		Graded aerobic exercise	
	Thrombosis	Passive movements, respiratory training, compression, positioning		Active dynamic muscular exercise, compression treatment	
Pain	Generalized pain (fibromyalgia-like symptoms)	Physical modalities	Graded activities	Aerobic exercise, muscle balancing, cognitive behavioral treatment	
Mental health	Depression, anxiety	Coping strategy	Coping strategy, exercise	Exercise, psychotherapy	Social reintegration
Autonomous regulation	Fatigue, reduced general physical performance, sleep disorders	Passive physical stimuli	Passive physical stimuli, graded exercises	Aerobic training, sleep hygiene, coping strategies	

surveys on Cochrane Rehabilitation.[22] Of course selection of treatments and intensity must be individually adapted by skilled rehabilitation physicians, and team integrated rehabilitation will be essential. All of the rehabilitation interventions should be supported with well-defined functional assessment by physical and rehabilitation medicine (PRM) physicians. The functional assessment, particularly at acute and early acute phases, should consider comorbid aspects that could lead to pneumonia and mortality; functional impairment (existed and impending) which is caused by SARS-CoV-2 infection; actual functional capacities that could support the recovery process and improvement of quality of life.[23] It is also important to stress that the long term dysfunction has a high impact on the quality of life and participation (i.e. unfitness for work). This also is a strong argument of why rehabilitation must be provided for patients after COVID-19.[24]

From the perspective of care planning it is recommended to set-up specialized rehabilitation centers (within existing rehabilitation units), and to build up networks of partners in the community. Teleconsulting and telerehabilitation will be core elements to adequately manage the complex problems as well as the growing number of persons with a need for acute rehabilitation and suffering from long-term symptoms.[25]

Taken together, rehabilitation plays a major role in managing the health-related issue of COVID-19 patients for both hospitalized and discharged patients. However, rehabilitation interventions in this situation are quite complex and need well-trained professionals. This is due to the complex of hygiene regulations, specific training, and personal protective equipment that are needed to handle this specific group of patients.

In addition to the above-mentioned problems, participation is also a problem for post-COVID-19 patients, which include unfitness to work and other social integration issues. These also should be managed by vocational rehabilitation, stepwise re-integration, social activities, and family-oriented psychotherapy.

THE EFFECTS OF REDUCING THE CAPACITY OF REHABILITATION SERVICES FOR OTHER PATIENTS (NON-COVID-19) IN NEED FOR REHABILITATION (E.G PEOPLE WITH DISABILITY, PATIENT WITH CHRONIC DISEASES (E.G. CANCER, TRAUMATIC BRAIN INJURY, SPINAL CORD INJURY, STROKE, DIABETES, CHRONIC PAIN, ETC)

As aforementioned, rehabilitation services have been disrupted during COVID-19, including in Indonesia. Not only in top referral hospitals but also in rehabilitation practices (e.g. PRM practices, physiotherapy practices, etc.) have reduced the capacity during the COVID-19 pandemic. This capacity reduction is not only because of prevention of the spreading the SARS-COV-2 infection, but also the need of hygiene and special personal protective equipment. These increase the health cost, too. Because of these issues, many non-COVID-19 patients who are in need of rehabilitations have delayed of treatment that could lead to complications and consequently increase the functioning deficits.

In addition to the existing patients who are in need of rehabilitation, such as stroke, musculoskeletal, cancer and cancer survivor, spinal cord injury, diabetes, and others, the COVID-19 patients (both in and outpatients) need to have special concerns. As aforementioned, COVID-19 patients and their survivors need multi-rehabilitation interventions from a multi-professional team in rehabilitation. These should also take into account when prioritizing and managing patients in rehabilitation needs.

SITUATION, CHALLENGES, AND RECOMMENDATION OF REHABILITATION MEDICINE IN LONG-TERM COVID-19 PANDEMIC IN INDONESIA

It is predicted that COVID-19 will last longer.[26] It means, a different aspects of life will be affected. From an economic perspective, long-term COVID-19 can lead also to poverty.[27] As it is known, poverty and disability are bidirectional.[28] Therefore in the long-term pandemic, it will increase also the prevalence of disability worldwide, including in Indonesia.

Prior to the pandemic of COVID-19, health-related issues in Indonesia still needed to be improved, including in the field of rehabilitation

medicine.[29] The issue was not only the lack of health professionals but also health provisions. These issues are also worsened due to an uneven distribution of both rehabilitation professionals and rehabilitation provision all over Indonesia,[29] which are being taken into consideration and improved by The National Organization of the Indonesian Physical Medicine and Rehabilitation Specialists through several strategic plans.

As rehabilitation can shorten the length of stay in all phases of healthcare, optimize health outcomes, avoid re-admission, reduce health care and social cost, increase the employment rate for COVID-19 survivors, and strengthen the health care workforces, therefore, in order to achieve the highest level and quality of rehabilitation services during (and in the cases of long-term) COVID-19, some recommendations need to be considered. The following are generic list recommendations in the field of rehabilitation medicine based on practical and opinion of authors at different levels of health systems.

At the Government Level

1. As suggested by WHO11, rehabilitation should be included as an integral part of the national strategy for the COVID-19 pandemic.
2. Improve rehabilitation capacity and rehabilitation service-related financing for COVID-19 patients.
3. Ensure that other persons in need for rehabilitation get access to good quality rehabilitation services.

At the Hospital Level

1. Make available rehabilitation services at all phases of health care (acute to long-term) in the COVID-19 referral hospitals (early rehabilitation and outpatient services).
2. In the case of insufficiency, prioritize patients based on needs and the risk of having complications.
3. Increase the capacity of rehabilitation services in order to treat other non-COVID-19 patients with rehabilitation needs.
4. Implement telerehabilitation as a complementary treatment for patients.
5. Implement prevention and rehabilitation programs for health workforces who are in charge of COVID-19 patients.
6. Include hygiene and personal protection equipment when treating COVID-19 patients.

At Health Professional Level

1. Rehabilitation professionals should collaborate with all other health professionals in order to achieve an effective and optimal health outcomes in general (inter-professional).
2. Collaboration with health rehabilitation professionals to deliver quality rehabilitation services (team integration/multi-professional rehabilitation).
3. In order to fill in the gap of health professionals in rehabilitation, training basic rehabilitation programs related to the symptoms of COVID-19 patients for other health professionals, like nurses, general practitioners, and others such as CBR workers, family, and others are needed for treating recovered patients.

CONCLUSION

Hopefully, the presented situation of COVID-19 pandemic and rehabilitation medicine in Indonesia, as well as list of recommendations, can be considered in managing the COVID-19 pandemic by relevant stakeholders.

REFERENCES

1. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71-6.
2. Ovali F. SARS-CoV-2 infection and the newborn. Front Pediatr. 2020;8:294.
3. Lloyd-Sherlock P, Ebrahim S, Geffen L, McKee M. Bearing the brunt of covid-19: older people in low and middle income countries. BMJ. 2020;368:m1052.
4. Lithander FE, Neumann S, Tenison E, et al. COVID-19 in older people: a rapid clinical review. Age Ageing. 2020; 49:501-15.
5. Fuellen G, Liesenfeld O, Kowald A, et al. The preventive strategy for pandemics in the elderly is to collect in advance samples & data to counteract chronic inflammation (inflammaging). Ageing Res Rev. 2020: 101091.
6. Katulanda P, Dissanayake HA, Ranathunga I, et al. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. Diabetologia. 2020.

7. Martini N, Piccinni C, Pedrini A, Maggioni A. CoViD-19 and chronic diseases: current knowledge, future steps and the MaCroScopio project. Recent Prog Med. 2020;111:198-201.
8. COVID-19 STP. Peta sebaran COVID-19. cited on 21 August 2020. Available from: https://covid19.go.id/peta-sebaran.
9. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. JAMA. 2020.
10. worldometers.info. COVID-19 Coronavirus pandemic. cited on: 8 September 2020. Available from: https://www.worldometers.info/coronavirus/.
11. WHO. COVID-19 significantly impacts health services for noncommunicable diseases. cited on: 20 August 2020. Available from: https://www.who.int/news-room/detail/01-06-2020-covid-19-significantly-impacts-health-services-for-noncommunicable-diseases.
12. Channappanavar R, Perlman S. Evaluation of activation and inflammatory activity of myeloid cells during pathogenic human Coronavirus infection. Methods Mol Biol. 2020;2099:195-204.
13. Lau SKP, Lau CCY, Chan KH, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J Gen Virol. 2013;94:2679-90.
14. Lopez M, Bell K, Annaswamy T, Juengst S, Ifejika N. COVID-19 Guide for the rehabilitation clinician: A review of nonpulmonary manifestations and complications. Am J Physic Med Rehab. 2020;99:669-73.
15. Orsini A, Corsi M, Santangelo A, et al. Challenges and management of neurological and psychiatric manifestations in SARS-CoV-2 (COVID-19) patients. Neurol Sci. 2020;41:2353-66.
16. PAHO. Rehabilitation considerations during the COVID-19 outbreak 2020; 2020.
17. Gomez-Rial J, Rivero-Calle I, Salas A, Martinon-Torres F. Role of monocytes/macrophages in Covid-19 pathogenesis: Implications for therapy. Infect Drug Resist. 2020;13:2485-93.
18. Chowdhury MA, Hossain N, Kashem MA, Shahid MA, Alam A. Immune response in COVID-19: A review. J Infect Public Health. 2020.
19. Bhaskar S, Sinha A, Banach M, et al. Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM consortium position paper. Frontiers Immunol. 2020;11:1648.
20. Belli S, Balbi B, Prince I, et al. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived the hospitalisation. Eur Respir J. 2020.
21. Lopez C, Closa C, Lucas E. Telemedicine in rehabilitation: Post-COVID need and opportunity. Rehabilitacion (Madr). 2020.
22. Rehabilitation C. Cochrane rehabilitation. Cited on: 21 August 2020. Available from: https://rehabilitation.cochrane.org/.
23. RSCM. Covid-19 clinical practice guideline. Jakarta: RSCM, 2020.
24. Gutenbrunner C, Stokes EK, Dreinhofer K, et al. Why rehabilitation must have priority during and after the COVID-19-pandemic: A position statement of the Global Rehabilitation Alliance. J Rehab Med. 2020; 52: jrm00081.
25. Salawu A, Green A, Crooks MG, Brixey N, Ross DH, Sivan M. A proposal for multidisciplinary tele-rehabilitation in the assessment and rehabilitation of COVID-19 survivors. Int J Environ Res Public Health. 2020;17.
26. Helmholtz. Is it possible to predict an end to the corona crisis? Cited on: 21 August 2020. Available from: https://www.helmholtz.de/en/health/is-it-possible-to-predict-an-end-to-the-corona-crisis/.
27. Bank TW. Projected poverty impacts of COVID-19 (coronavirus). Cited on: 21 August 2020. Available from: https://www.worldbank.org/en/topic/poverty/brief/projected-poverty-impacts-of-COVID-19.
28. UN. Realization of the sustainable development goals by, for and with persons with disabilities. 2018; New York: United Nations; 2018.
29. Nugraha B, Setyono GR, Defi IR, Gutenbrunner C. Strengthening rehabilitation services in Indonesia: A brief situation analysis. J Rehab Med. 2018;50:377-84.

The Management of Cytokine Storm in COVID-19

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ABSTRAK

Badai sitokin pada infeksi COVID-19 adalah keadaan dimana terjadi respons imun yang berlebihan terhadap adanya stimulus dari luar dengan patogenesis yang kompleks. Badai sitokin menyebabkan terjadinya perburukan penyakit yang terjadi secara cepat dengan angka mortalitas yang tinggi. Bukti yang ada menunjukkan bahwa progresivitas penyakit berkaitan erat dengan adanya peningkatan sitokin pada pasien pneumonia akibat SARS-CoV2. Terapi yang efektif dan aman dibutuhkan untuk mengatasi hiperinflamasi sehingga diharapkan dapat mencegah terjadinya kematian. Hingga saat ini belum ada terapi yang spesifik untuk mengatasi infeksi COVID-19. Studi pendahuluan telah memperlihatkan bahwa terapi dengan imunomodulator dan terapi imunosupresif dapat dipertimbangkan sebagai terapi pilihan pada infeksi COVI-19 yang berat. Dalam artikel ini diulas mengenai patogenesis terjadinya badai sitokin pada infeksi COVID-19 beserta terapinya, sehingga diharapkan dapat digunakan sebagai pedoman dalam tatalaksana pasien.

Kata kunci: *badai sitokin, hiperinflamasi, COVID-19.*

ABSTRACT

Cytokine storm in COVID-19 infection is an excessive immune response to external stimuli where the pathogenesis is complex. The disease progresses rapidly and the mortality is high. Certain evidence shows that the severe deterioration of some patients has been closely related to the strong upregulation of cytokine production in SARS-Co-V2 induced pneumonia with an associated cytokine storm syndrome. Identification of existing approaved therapy with proven safety profile to treat hyperinflammation is critical unmet need in order to reduce COVID-19 associated mortality. To date, no specific therapeutic drugs are available to treat COVID-19 infection. Preliminary studies have shown that immune-modulatory or immune suppressive treatments might be considered as treatment choices for COVID-19, particularly in severe disease. This article review the pathogenesis and treatment strategies of COVID-19 virus-induced inflammatory storm in attempt to provide valuable medication guidance for clinical treatment.

Keywords: *cytokine storm, hyperinflammation, COVID-19.*

INTRODUCTION

Cytokine storm (CS) refers to excessive and uncontrolled release of proinflammatory cytokine. Clinically it commonly presents as systemic inflammation, multiple organ failure and high inflammatory parameters. While most patients with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop severe disease that requires hospitalization and oxygen support

and 5% have critical disease with complication such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, acute kidney injury, cardiac injury and multiple organ failure. Older age, smoking and underlying noncommunicable diseases such as hypertension, cardiac disease, chronic lung disease and cancer have been reported as risk factors for severe disease and death. Multivariate analyses have confirmed that older age, higher sequential organ failure assessment (SOFA) score and D-dimer > 1μg/L on admission were associated with higher mortality. The effective antiviral responses of the host innate and adaptive immunity, including the production of various proinflammatory cytokines, the activation of T cells, CD4 and CD8+ T cells are essential for controlling the viral replication, limiting the spread of virus, inflammation and cleaning the infected cells.[1,2]

PATHOGENESIS

Virus SARS-CoV-2 transmitted via droplet, direct contact and fomites. Mediated by transmembrane protease serine-type 2 (TMPRSS2), SARS-CoV-2 S protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter and infect cells. Viral entry followed by replication RNA genomes translation. Ribonucleic acid synthesis occurs on the cellular membrane to mediate the viral replication and form a new virus. Angiotensin-converting enzyme 2 presents on the oral and nasal mucosal, nasopharyngeal, lung, stomach, small intestine and large intestine. skin, thymus, bone marrow, spleen, liver, kidney, brain, blood vessels endothelial cells and smooth muscle cells.[3] Multiplication progressed in the lower respiratory tract and the gastrointestinal mucosa causing slight viremia. With adequate immunity to handle the infection process, the patient may appear asymptomatic.[4] The effective antiviral respons of the host innate and adaptive immunity are essential for controlling the viral replication, limiting the spread of virus, inflammation and cleaning the infected cells. A rapid and well-coordinated innate response is the first line of defense against viral infection. However, dysregulated and excessive immune respons may cause immune damage to the human body. Furthermore, the tissue injury caused by the virus could induced the exaggerated production of proinflamatory cytokines, recruitment of proinflamatory macrophages and granulocytes. This may results in cytokines storm termed as macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis leading to further tissue damage.[5] A cytokine storm is the primary mechanism of ARDS due to uncontrolled systemic inflammation induces by proinflammatory cytokines (IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α,) and chemokines. The plasma level of IL-6 considered as a significant cytokine contributing to MAS, increased in patients with severe COVID-19 infection.[5] Increasing of inflammatory cytokine release due to uncontrolled activation of immune reponses is likely not limited to the innate mechanisms. As a result of proinflamatory cytokine expression and the presence of nuclear antigen from cell and tissue damage, adaptive immune cells may become activated and trigger a second wave of inflammation potentially in patients who deteriorate after 7 - 10 days of infection. Indeed, adaptive immune cells, namely T lymphocytes which are observed in lung tissue sections of COVID-19 patients with ARDS, may drive inflammation at later disease stages.[6]

CLINICAL MANIFESTATIONS

Infection of COVID-19 exhibits 3 grades of increasing severity, which correspond with distinct clinical findings, response to therapy and clinical outcome (**Figure 1**).[7,8]

Stage I (Mild) – Early Infection

The initial stage occurs at the time of inoculation and early establishment of disease. For most patients, this involves an incubation period associated with mild and often non-specific symptoms, such as malaise, fever and a dry cough. During this period, SARS-CoV-2 multiplies and establishes residence in the host, primarily focusing on the respiratory system. Initially SARS-CoV-2 binds to its target using the angiotensin-converting enzyme 2 receptor on human cells. These receptors are abundantly present on human lung and small intestine

epithelium and the vascular endothelium. As a result of the airborne method of transmission and affinity for pulmonary angiotensin-converting enzyme 2 receptors, the infection usually presents with mild respiratory and systemic symptoms.

Stage II (Moderate) – Pulmonary Involvement (IIa) Without and (IIb) With Hypoxia

In the second stage of establishes pulmonary disease, viral multiplication and localized inflammation occur in the lung tissue. During this stage, patients develop a viral pneumonia with cough, fever and possibly hypoxia (defined as PaO2/FiO2 <300 mmHg). Imaging with chest roentgenogram or computed tomography reveals bilateral infiltrates or ground-glass opacities. Blood tests reveal increasing lymphopenia, along with elevation of makers for systemic inflammation. It is at this stage that most patients with COVID-19 would need to be hospitalized for close observation and management.

Stage III (Severe) – Systemic Hyperinflammation

A minority of COVID-19 patients will transition into the third and most severe stage of the illness, which manifests as an extrapulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation seem to be elevated. COVID-19 infection results in a decrease in helper, suppressor and regulatory T cell counts. Studies have revelaled that inflammatory cytokines and biomarkers such as IL-2, IL-6, IL-7, TNF- α, granulocyte colony-stimulating factor, macrophage inflammatory protein 1, C-reactive protein, ferritin and D-dimer are significantly elevated in those patients with more severe disease. A form akin to secondary hemophagocytic lymphohistiocytosis may occur in patients in this advanced stage of the disease. In this stage, shock, vasoplegia, respiratory failure and even cardiopulmonary collapse are discernable. Systemic organ involvement, even myocarditis would manifest during this stage.

DIAGNOSIS

Patients with confirmed COVID-19 infection may have severe cytokine release syndrome with the following criteria: persistent fever for more than 3 days, two biomarkers elevation (cytokines, CRP, ferritin) and at least one organ toxicity (hypotension that requiring vasoactive drugs, hypoxia [SpO2 < 90% in room air]) and neurologic disorder including mental status changes, obtundation and seizure. Cytokines and CRP examination can serve as a diagnostic tool to determine the disease severity. Ideally, cytokines profile examination should be performed in order to determine the most suitable immunomodulator treatment . In the acute phase, the liver responds to IL-6 activity by synthesizing CRP.[9,10] C-reactive protein examination is useful

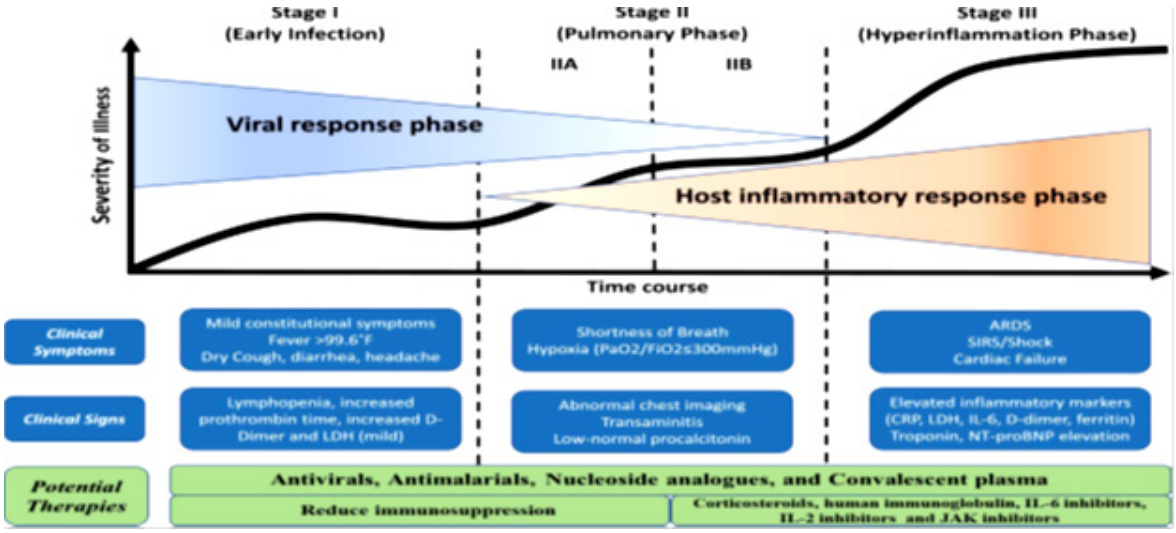

Figure 1. Classification of COVID-19 disease states and potential therapeutic targets.

to monitor the progress of the disease, faster to examine, economical and widely available compared to cytokine levels measurement. Clinical symptoms approach and biomarker examination are usefull to predict the severity of disease. Chest X-ray examination may reveal diffuse infiltrate on both lung and from lung CT scan may also show diffuse ground-glass opacity on both lung with or without crazy-paving pattern consistent with ARDS.[9,10]

TREATMENT

Drugs for COVID-19 infection treatment mostly come from observational study with few clinical trials without provide high-quality evidence. Based on WHO guideline for clinical management of COVID-19, treatment with antiviral and immunomodulator should be in context of clinical trial. Therefore for the legal aspect, outside of clinical trial the the investigational therapeutics should be given with the following criteria: treatment has been suggested by qualified scientific advisory committee on the basis of a favourable risk-benefit analysis, as well as an appropriately qualified ethics committee have approved such use, the patiets informed consent is obtained and the emergency use of the drugs is monitored and the results are documented and shared in timely manner with the wider medical and scientific community.[1] Principally, cytokine storm treatment mainly focused on immunosuppression alongside control measures on triggering factors. Drugs given to COVID-19 infection consisting of antiviral therapy, corticosteroid, antibiotic, venous thromboembolism prophylaxis and therapy with immunomodulators (chloroquine/ hydroxychloroquine, azithromycin, tocilizumab, intravenous immunoglobulin (IVIG), plasma convalescen therapy and stem cells therapies). Beside such medical treatment, supportive treatment with oxygen therapy, noninvasive ventilation and ventilatory support should be performed simultaneously according to the severity of the disease.[1,11]

Antiviral Therapy

At present, there is no definitive antiviral treatment for COVID-19. Available drug options that come from the clinical experience of treating SARS, MERS and other previous Influenza virus have been used for treatment of COVID-19 patients. Lopinavir as a proteinase inhibitors, restains the action of 3-chymotrypsin-like protease (3CLpro) that plays an important role in processing the viral RNA, and disrupts viral replication process and their release from host cells. Its usually combined with ritonavir that can enhance the antiviral activity of lopinavir. The recommended regimen is lopinavir 200 mg/ritonavir 50 mg, 2 tablets twice daily for 14 days or for 7 days after become asymptomatic. Favipiravir an oral antiviral drug, is a synthetic prodrug of a purine nucleotide. It undergoes intracellular ribosylation and phosphorylation into the active form of favipirapir ribofuranosyl-5'-triphosphate (favipirapir-RTP). Favipirapir-RTP can inhibits RNA-dependent RNA polymerase (RdRp) activity, resulting in inhibition of transcription and replication of the viral genome. Favipiravir is given orally for 7 – 10 days, a maximum of 14 days with a loading dose 1600 mg every 12 hours for the first day, followed by a maintenance dose 600 mg every 12 hours (days 2 to 7 or 10). Remdesivir is prodrug of adenosine analogue that undergoes metabolism to an active C-adenosine nucleoside triphosphate anolaque. The active form (Favipirapir-RTP) competes with adenosine triphosphate and incorporates with the RNA strand, causing premature termination or RNA synthesis and halting the RNA replication. The initial dose is a single 200 mg loading dose, followed by 100-mg daily infusion for 9 days.[11-13]

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have been used in treating COVID-19 infection with the following actions: (1) immunomodulatory effects through inhibition of cytokine production. It can inhibit TLR-7 and TLR-9 signaling pathway and decrease the secretion of proinflamatory cytokines (IL-6, TNF-α, IL-1 and IFN-γ); (2) impairing lysosomal and autophagosome functions and subsequently immune activation; (3) inhibition of proteolytic processing and endosomal acidifation; (4) antiviral effects including impairment of viral replication,

interference with posttranslational modification of viral proteins, and inhibition of binding of viral particle to cellular receptors and (5) blocking virus-cell fusion and interference with glycosylation of SARS-CoV and ACE2 cellular receptors. The recommended dosage for Chloroquine is as follows : If the body weight is more than 50 kg, 500 mg twice daily is given for 7 days coarse of treatment. For body weight less than 50 kg, 500 mg twice daily is given for the first second days, followed by 500 mg once daily on the third to seventh days. For hydroxychloroquine the recommendation dosage is 400 mg given twice daily for the first day, followed by 200 mg twice daily for another 6 days.[11,13]

Azithromycin

Azithromycin is a macrolide antibiotic that has several actions including: (1) antimicrobial activity against Gram positive and Gram negative bacterial as well as atypical pathogens; (2) anti-inflamatory activity as it has been shown to reduce the blood levels of proinflamatory cytokines and chemokines; (3) immunomodulatory actions; and (4) antiviral activity as it has been shown to have in vitro activity against Zika and Ebola viruses. In pateints with COVID-19 infections, several studies have shown efficacy of azithromycin particularly when given in combination with chloroquine or hydroxychloroquine. The recommended dose of azithromycin is 500 mg once daily for 7 days.[11-13]

Corticosteroids

Corticosteroids are useful in the treating of a cytokine storm. Indication for corticosteroids treatment are acute hypoxemic respiratory failure, requirement for mechanical ventilation and another accepted indication for example COVID patients with asthma or COPD exacerbation. Another indication to administer corticosteroids includes a severe and critical clinical state, persistent fever (>39 ^{0}C), rapid deterioration suggested by CT-scan findings (more than 50% of the infected area on CT-scan images within 48 hours), plasma concentration of inflamatory cytokine, such as IL-6 $\geq$ 5 times above the upper limit of normal and patients not responding to anti IL-6 treatment. Dexamethasone 6 mg daily for 10 days is strongly recommended based on RECOVERY trial. The median duration of steroids treatment in that study was only 7 days. Therefore if patients are already improving, the corticosteroids treatment may be safe to stop prior to 10 days. Higher doses of corticosteroids (dexamethasone 10-20 mg daily or equivalent doses of methylprednisolone) could be considered in patients with severe ARDS. If higher dose corticosteroids are used, the dose may be reduced to 6 mg dexamethasone daily or equivalent as soon as improvement occurs. Dexamethasone has a long biological half-life with its auto-tapper property and thereby prevent rebound inflammation.[1]

Venous Thromboembolism (VTE) Prophylaxis

Most patients with cytokine storm due to COVID-19 infection seem to be extremely hypercoagulable. This would support a potential role for VTE prophylaxis in COVID-19 infection. Enoxaparin 30 SC mg bid is suggested as preferred dose for VTE prophylaxis in critically ill patients with COVID-19. Enoxaparin 30 mg SC bid should also be considered for VTE prophylaxis in hospitalized ward-based patients. Higher doses of anticoagulant prophylaxis (enoxaparin 0.5 mg/kg BW SC bid) may be considered in patients with moderately elevated D-dimer (1500 ng/ml) and for patients with weight above 100 kg or BMI above 40 kg/m^2. Check an Xa level four hours after the third dose, targeting a level of 0.5-0.8 IU/ml.[1]

Antibiotic Treatment

For patiens with severe disease, early and appropriate empiric antimicrobial therapy should be based on the clinical diagnosis, local epidemiology and susceptibility data and national treatment guideline. Antibiotic should be given as soon as possible (within 1 hour of initial assessment if possible), ideally with blood cultures obtained first. Empiric antibiotic therapy should be de-escalated on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching of intravenous to oral route of administration and provide targeted treatment based on microbiologic results.[1]

IL-6 Inhibitor

Tocilizumab is an IL-6 receptor inhibitor, which acts to interrupt IL-6 signals to immune effector cells, hence decreases the immune activation and alleviates the inflammatory processes. The recommended dose is 4-8 mg/kg BW. The recommended dose is 400 mg with 0,9% saline diluted to 100 ml. The infusion time is more than 60 minutes. For patients with poor efficacy of the first dose, an additional dose can be given with the same as initial dose after 12 hours. No more than 2 doses should be given. Maximum single dose is 800 mg.[11-13]

Intravenous Immunoglobulins (IVIG)

Intravenous immunoglobulins is a blood preparation isolated and concentrated from healthy donors consisting of over 95% of IgG and trace amounts of IgM or IgA. Potential antiinflamatory and immunomodulatory mechanisms of high-dose IVIG therapy are by neutralization of pathogenic antigens through the F(ab)'2-mediated mechanisms, immunomodulatory effects on endothelial cells, innate and adaptive immune cell through Fc-mediated mechanisms and neutralization of endogenous antigen including proinflamatory cytokines, chemokine and complement fragment. The suggested dose of IVIG is 0.3 - 0.5 g/kg BW/day for five days. Most of the research concluded immunoglobulin administration is effective and tolerable, but some also reported side effects occurring after the drug administration.[13-16]

Convalescent Plasma

Curently, convalescent plasma has been added to the existing treatments in patients who were unresponsive to the existing protocol. The efficacy of convalescent plasma would be improved with correct indication and timing. Theoretically, convalescent plasma is suitable to treat the disease in initial symptomatic phase.[17] The decision for the treatment of COVID-19 patients with convalescent plasma should be approved by a critical care specialist. This treatment is recommended to the confirmed case (positive result with PCR-test) or probable case (clinical/radiological evidence compatible with COVID-19, but PCR-test result not yet available), patients with COVID-19 who are above 18 years old within the first 14 days of the disease and 7 - 19 days after the symptoms start. The recommended minimum dose for one patients is one unit (200 ml per unit) convalescent plasma. Second unit can be administered 48 hours following the completion the transfusion of the first unit of convalescent plasma and can be administered up to maximum of 3 units (600 ml). The decision for total dose is taken by the physician in charge and based on the clinical findings to avoid volume overload in patients who are instable in term of cardiopulmonary functions. Neutralizing antibodies (NAbs) are crucial in virus clearance and have been considered essential in protecting against viral disease. Antiviral effects of NAbs IgG and IgM are the main isotypes, although IgA may be also important particularly in mucosal viral infections. Passive immunity driven by convalescent plasma therapy can provide these NAbs that restrain the infection. The efficacy of this therapy has been associated with the concentration of NAbs in plasma from recovered donors. Immunomodulation is another possible action of convalescent plasma by controlling an overreactive immune system. The benefit of convalescent plasma therapy is greater when it is used in a timely manner in the early viremic phase as its main action is through direct neutralization of the virus, whereas the use of IVIG administration may be usefull even in a more tardive phase as its principal mechanism is to counteract the deleterious effects of the dysregulated immune respons.[15-18]

Mesenchymal Stem Cell Therapies

Mesenchymal stem cell (MSC) and their secretory products in the treatment of severe COVID-19 infections have the following beneficial effects therapies : (1) Suppression of viral replication, viral shedding and virus-induced damage to lung epithelial cells; (2) enhancement of the generation of regulatory T-cells that are suppressed by COVID-19; (3) MSCs modulate the proliferation and activation of naïve and effector T-cells, NKCs and mononuclear cells; (4) MSCs prevent the formation of NETs that may have deletetious effects in the patients with COVID-19 pneumonia; (5) MSCs can inhibit

the cytokine storm induced by COVID-19; (6) secretomes of MSCs have antiviral, antibacterial and even analgesic effects; (7) reduction in pulmonary edema associated with ARDS in COVID-19; (8) enhancement of tissue regeneration and promotion of endogenous repair and healing in ALI induced by COVID-19. MSCs at dose of 1 x 106 cells/kg body weight, administered intravenously. MSC are suspended in 100 ml saline and injected over 40 minutes.[19-20]

Oxygen Treatment

In selected patients with mild ARDS, high flow nasal canule (HFNO), non-invasive ventilation-continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) can be used. Compared with standard oxygen therapy, HFNO may reduce the need for intubation. Adult HFNO systems can deliver 60 L/min of gas flow and FiO2 up to 1.0. Patients receiving HFNO or NIV should be in monitored setting and care for by personnel experienced with HFNO and or NIV and capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after 1 hour. In this case intubation should not be delayed. Patients with hypercapnia, haemodinamic instability, multiorgan failure or with abnormal mental status should not receive HFNO. High flow nasal canule and NIV should be used in isolation room with airborne precautions. If HFNO and CPAP are not available, oxygen is delivered via face mask with reservoir bag (flow rates of 10-15 L/min, which is tipically the minimum flow required to maintain bag inflation with FiO2 0.60-0.95). Intubated patients should use low tidal volume (4-8 ml/kg predicted body weight and lower inspiratory pressure /plateau pressure < 30 cmH2O). In severe ARDS (PaO2/FiO2 < 150) prone ventilation for 12-16 hours per day is recommended. In moderate or severe ARDS a higher positive end-expiratory pressure (PEEP) is suggested. Titration of the PEEP is performed individualized with monitoring for beneficial and harmful effect. In patients with moderate-severe ARDS (PaO2/FiO2 < 150), neuromuscular blockade by continuous infusion should not be routinely used. Avoid disconnecting the patien from the ventilator wich results in loss of PEEP, atelectasis and increased risk of infection of health care workers. Consider to refer patients who have refractory hypoxaemia (PaO2/FiO2 < 50 mmHg for 3 hours or < 80 mmHg for > 6 hours) despite lung protective ventilation to access treatment with extracorporeal membrane oxygenation (ECMO). Extracorporeal membrane oxygenation is a resource-intensive technique restricted to specialized centers, and it remain an extremely limited resource. Therefore its use as a rescue should be reserved for carefully selecterd patiens.[1]

PROGNOSIS

In general, the prognosis of ARDS in COVID-19 infection is depend the severity of the disease. Patients with mild ARDS usually have favorable outcome with early medical and supportive treatment. The condition of the patients may be reversible if administered therapy showed an acceptable response. However, ARDS due to cytokine storm can be severe and life-threatening, leading to multi-organ failures even with agresif medical treatment. Neurologic disorders occurring in this syndrome may be reversible but can indicate a dangerous complication of cerebral edema or brain stem death.[9]

REFERENCES

1. Clinical management of COVID-19. Interim Guidance. Geneva : World Health Organization; 2020.
2. Qing Ye, Bili Wang, Jianhua Mao. The pathogenesis and treatment of the cytokine storm in COVID-19. J Infect Dis. 2020. doi.org/10.1016/j.jinf.2020.03.037.
3. Mousavizadeh L, Ghasemi S, Genotype and phenotype of COVID-19: Their roles in pathogenesis. J Microbiol Immunol Infect. 2020. doi.org/10.1016/j.jmii.2020.03.022.
4. Singh VK, Mishra A, Singh S, Kumar P, Singh M, Jangannath C, Khan A. Emerging prevention and treatment strategies to control COVID-19. Pathogen. 2020;9;2-16.
5. Tufan A, Guler AA, Cerinic MM. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci. 2020;50:620-30.
6. Felsenstein S, Herbert J, McNamara P, Hedrich CM. COVID-19: Immunology and treatment options. Clin Immunol. 2020. doi.org/10.1016/j.clim.2020.108448.
7. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Hearth Lung Transplant.

2020;39:405-7.
8. COVID-19: Pathogenesis, cytokine storm and therapeutic potensial of interferons. Cytokine Growth Factor Rev. 2020. doi.org/10.1016/j.cytogfr.2020.05.002.
9. Roche AG. Cytokines release syndrome, reviewing a new entity in the intensive care unit. Med Intensiva. 2019;43 (8):480-8.
10. Gupta KK, Khan MA, Singh SK. Constitutive inflammatory cytokines storm: A major threat to human health. J Interfer Cytokine Res. 2020;40 (1):1-5.
11. Instiaty, Darmayani I G A P. Marzuki JE, et al. Antiviral treatment of COVID-19: clinical pharmacology narrative review. Med J Indones. 2020.
12. Sanders JM, Monogue ML, JodlowskiTZ, Cutrell JB. Pharmacologic treatment for Coronavirus disease 2019 (COVID-19). JAMA. 2020;323:1824-36.
13. Delang L, Neyts J. Medical treatment options for COVID-19. Eur Heart J: Acute Cardiovas Care. 2020; 9: 209-14.
14. Murthy H. Cytokines release syndrome: Current perspectives. Immuno Targers Ther. 2019;8:43-52.
15. Iannaccone G, Scacciavillani R, Del Buono MG, et al. Weathering the cytokine storm in COVID-19: Therapeutic implication. Cardiorenal Med. Doi: 10.1159/000509483.
16. Cao W. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus disesase is 2019. Infect Dis Soc Am. 2020.
17. Xiaosheng Liu, Wei Cao, Taisheng Li. High-dose intravenous immunoglobulins in the treatment of sebere acute viral pneumonia: the known mechanism and clinical effect. Frontiers Immunology. Doi: 10.3389/fimm.2020.01660.
18. Chen L. Convalescent plasma as a potential therapy for COVID-19. Lancet. 2020; 0: 98-400.
19. Shen C. Treatment of 5 Critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020.
20. Al-Anazi KA, Al-Alnazi WK, Al-Jasser AM. Update on COVID-19 infections and the promising role of mesenchymal stem cell therapies in their management. 2020.