VOL. 43, NO. 3, July 2023

p-ISSN 0853-7704
e-ISSN 2620-3162

JURNAL RESPIROLOGI INDONESIA

Majalah Resmi Perhimpunan Dokter Paru Indonesia
Official Journal of The Indonesian Society of Respirology

Akreditasi RISTEKDIKTI
Surat Keputusan Menteri Riset dan Teknologi Nomor: 200/M/KPT/2020 Tanggal 23 Desember 2020, Peringkat 2
Website: http://www.jurnalrespirologi.org

JURNAL
RESPIROLOGI INDONESIA

Majalah Resmi Perhimpunan Dokter Paru Indonesia
Official Journal of The Indonesian Society of Respirology

SST : Surat Keputusan Menteri Penerangan RI
No.715/SK/DitjenPPG/SST/1980 Tanggal 9 Mei 1980

Editorial Office
PDPI Jl. Cipinang Bunder, No. 19, Cipinang Pulo Gadung
Jakarta Timur 13240 Telp: 02122474845
Email : editor@jurnalrespirologi.org
Website : http://www.jurnalrespirologi.org

Publisher
The Indonesia Society of Respirology (ISR)
Published every 3 months (January, April, July & October)

Jurnal Respirologi Indonesia
2nd Rank Accreditation
According to the Decree of the Minister of Research and Technology/Head of the National Research and Innovation Agency of the Republic of Indonesia Number: 200/M/KPT/2020
December 23, 2020

Petunjuk bagi Penulis

Jurnal Respirologi Indonesia adalah publikasi triwulan yang menerbitkan karya asli yang relevan dengan bidang kesehatan pernapasan.

Petunjuk pengiriman makalah

1. Makalah yang dikirim hendaklah makalah yang belum pernah diterbitkan dalam jurnal lain. Makalah yang pernah dipresentasikan secara lisan, dapat dikirimkan dengan memberikan catatan kaki pada halaman pertama mengenai waktu dan tempat makalah tersebut dipresentasikan.
2. Jurnal Respirologi Indonesia menerbitkan hasil penelitian, laporan kasus, tinjauan pustaka, perkembangan ilmu pengetahuan dan tulisan ilmiah lainnya.
3. Semua makalah yang dikirimkan pada redaksi, akan diseleksi dan disunting (edit) oleh tim redaksi. Apabila makalah memerlukan perbaikan isi, maka akan dikembalikan kepada penulis untuk diperbaiki.
4. Semua makalah, gambar/foto yang masuk ke redaksi akan menjadi hak milik redaksi dan tidak akan dikembalikan kepada penulis. Makalah yang dikirimkan harus disertai surat pengantar, dengan nama penulis dan gelar akademik tertinggi, instansi tempat penulis bekerja, nama dan alamat korespondensi, nomor telepon, nomor faksimili dan alamat email. Surat pengantar ditandatangani penulis.
5. Makalah asli dikirimkan serta 1 buah fotokopi seluruh makalah termasuk gambar/foto dan *Compact Disc* (CD). Tulis nama program yang digunakan dan nama file pada label *Compact Disc* (CD).

Penulisan makalah

1. Makalah termasuk tabel, gambar dan daftar pustaka diketik 1,5 spasi pada kertas kwarto (ukuran 21,5x28 cm), dengan jarak tepi kiri dan kanan masing-masing 2,5 cm. Halaman pertama diawali dengan judul, kemudian nama penulis dan lembaga/ instansi kerja penulis, dilanjutkan dengan isi makalah. Setiap halaman diberi nomor secara berurutan dimulai dari halaman pertama sampai dengan halaman terakhir.
2. Judul singkat dan jelas dengan jumlah maksimal 20 kata.
3. Abstrak untuk artikel penelitian dan laporan kasus dibuat singkat dan jelas sehingga pembaca dapat memahami hal yang akan disampaikan tanpa harus membaca seluruh makalah. Abstrak dituliskan dalam bahasa Indonesia dan Inggris maksimal 250 kata dan dalam bentuk paragraf. Setiap paragraf mengandung makna, pesan atau satu kesatuan ekspresi pikiran, dibangun atas sejumlah kalimat. Untuk artikel penelitian, abstrak harus mengandung tujuan penelitian, metode, hasil dan kesimpulan. Abstrak disusun dengan urutan *Background* / Latar belakang, *Methods* / Metode, *Results* / Hasil dan *Conclusion* / Kesimpulan.
4. Kata kunci berupa kata-kata yang dapat membantu untuk indeks, umumnya 3-5 kata yang bersifat spesifik. Kata kunci dituliskan di bawah abstrak.
5. Makalah ditulis sesuai subjudul yang dibuat. Artikel penelitian disusun dengan urutan pendahuluan, metode, hasil, pembahasan, kesimpulan dan daftar pustaka. Untuk tinjauan pustaka, secara garis besar disusun sesuai urutan pendahuluan, isi, penutup / kesimpulan dan daftar pustaka; dengan kerangka isi disesuaikan bergantung apa yang akan diutarakan. Untuk laporan kasus, susunannya berupa pendahuluan, latar belakang, kasus, diskusi, kesimpulan dan daftar pustaka.
6. Penulisan makalah hendaknya menggunakan bahasa Indonesia yang benar mengikuti Pedoman Umum Ejaan Bahasa Indonesia yang disempurnakan. Sedapat mungkin pakailah istilah Indonesia menurut Pedoman Umum Pembentukan Istilah. Singkatan yang digunakan dalam makalah adalah singkatan yang sudah baku.
7. Tabel diberi nomor yang sesuai urutan dan diberi judul yang singkat. Penjelasan tabel dan singkatan yang tidak lazim yang ada dalam tabel dituliskan pada catatan kaki. Apabila tabel berupa kutipan dari tabel tulisan lain yang telah dipublikasikan, maka harus dituliskan dikutip dari (nama penulis dan daftar pustaka/nomor

daftar pustaka), serta ijin tertulis dari penerbit yang bersangkutan. Jumlah tabel dan gambar yang dilampirkan maksimal 6 buah.

8. Gambar sebaiknya dibuat secara profesional, difoto dengan cetakan yang tajam dan jelas di atas kertas kilap, hitam putih/berwarna. Apabila gambar berupa gambar/grafik/ilustrasi yang pernah dipublikasi, maka harus dituliskan dikutip dari (nama penulis dan daftar pustaka/ nomor daftar pustaka), disertai ijin tertulis dari penerbit yang bersangkutan. Setiap gambar diberi keterangan di belakangnya, mengenai nomor gambar sesuai tercantum di makalah, nama/judul gambar, nama penulis. Jumlah tabel dan gambar yang dilampirkan maksimal 6 buah.
9. Rujukan sebaiknya tidak melebihi 40 buah. Rujukan sebaiknya berasal dari terbitan dalam waktu 10 tahun terakhir. Rujukan dari Jurnal Respirologi Indonesia (JRI) sebaiknya diikutsertakan sesuai topik yang ditulis.
10. Rujukan ditulis sesuai aturan Vancouver, diberi nomor urut sesuai urutan pemunculan dalam makalah. Penulisan nomor rujukan dalam makalah dituliskan rinci sesuai rujukan dalam makalah dituliskan rinci sesuai rujukan dalam makalah dituliskan sebagai *superscript*, setelah tanda baca (titik, koma, dsb). Cantumkan semua nama penulis, kecuali bila lebih dari 6 orang, maka dituliskan sebagai berikut, 6 penulis pertama diikuti oleh dkk (et al). Hindari penggunaan rujukan yang berupa abstrak atau komunikasi pribadi. Apabila menggunakan rujukan yang sedang dalam proses publikasi tetapi belum terbit, maka dapat digunakan perkataan “dalam proses terbit” (in press). Pada prinsipnya cara penulisan daftar pustaka adalah sesuai Vancouver yang dapat diunduh dari http://www.scriptiesaver.nl/Vancouver%20stijl.pdf

Contoh cara menuliskan rujukan

Buku

Winn WC, Allen SD, Janda WM, Koneman EW, Procop GW, Schreckenberger PC, et al. Koneman’s color atlas and textbook of diagnostic microbiology. 5th eds. Philadelphia: A Wolters Kluwer Company; 2006. p.1065-92.

Buku dengan editor

Hopewell PC. Tuberculosis and other mycobacterial disease. In: Murray JF, Mason RJ, Broaddus VC, Nadel JA, editors. Textbook of respiratory medicine. 4 th edition. New York: WB Saunders Company; 2005.p.979-1043.

Jurnal

Edginton ME, Rakgokong L, Verver S, Madhi SA, Koornhof HJ, Wong ML, et al. Tuberculosis culture testing at a tertiary care hospital: options for improved management and use for treatment decisions. Int J Tuberc Lung Dis. 2008;12:786-91.

Tesis

Rassuna V. Pengamatan hasil akhir pengobatan tuberkulosis paru BTA negatif kasus baru di RS Persahabatan. Tesis Departemen Pulmonologi dan Ilmu Kedokteran Respirasi FKUI. Jakarta; 2008.

Organisasi sebagai sumber

World Health Organization. Global Tuberculosis Control 2009: epidemiology strategy financing. Geneva: WHO Press; 2009. p.11-32.

Perhimpunan Dokter Paru Indonesia. Tuberkulosis Pedoman diagnosis dan penatalaksanaan di Indonesia. Jakarta: Indah Offset Citra Grafika; 2006.p.1-8.

Materi Elektronik

The Highland Council. The Learning Environment. [Online].2010 [Cited 2011 November 28]. Available from:http://www.highlandschoolsvirtualib.org uk/ ltt/ inclusive_enjoyable/environment.htm

Sack K. With Medicaid cuts, doctors and patients drop out. The New York Times [Online]. 2010 Mar 16 [cited 2010 Mar 16]; Health:A1. Available from: http://www.nytimes.com/2010/03/16/health policy/16m edicaid.html?ref=health

Instruction for Authors

"JURNAL RESPIROLOGI INDONESIA" is a three monthly journal publication that publishes original articles relevant to respiratory health.

Paper submission

1. The submitted paper must never be published in other journal. Paper that has been presented orally, could be submitted by putting foot-notes on the first-page regarding time and place it was presented.
2. Jurnal Respirologi Indonesia publishes research reports, case reports, literature reviews, information on science development and other scientific papers.
3. All papers submitted to the editors will beselected and edited by the editors. If revision of the contents is needed, the paper will be returned to the authors.
4. All papers, picture/photos submitted to the editors will belong to the editors and will not be returned to the authors. The submitted paper should be accompanied by a cover letter, stalling names of authors and the highest academic degree obtained, institutions of the authors, name and address for correspondence, phone and facsimile number and e-mail address. The cover letter should be signed by the author.
5. Original paper and one copy of all paper including pictures/photos and Compact Disc (CD) should be submitted. Write name of the computer programs used and names of the files on the Compact Disc (CD) label.

Paper preparation

1. Paper including tables, pictures and references should be typed with 1.5 space on Q4 paper (21.5 x 28 cm) with distances from the left and right ends of 2.5 cm. The first page should be started with a title, followed by list of authors and their institutions and then the text. Each page should be numbered consecutively starting from the first page up to the last page.
2. The title should be brief and clear, with no more than 20 words.
3. Abstract of research article and case report should be made short and clear, but it should precise with enough information for the reader to understand the main points in the paper without having to read the whole article. Abstract should be written in Indonesian and English with no more than 250 words, and it is written in paragraph form. Each paragraph contains meaning, message or unified expression, built on sentences. For research articles, the abstract should include objective, methods, main findings and main conclusions. Abstract should be written follow by Background, Methods, Results and Conclusion.
4. Keyword that will assist indexer in cross-indexing the articles, generally consists of 3-5 specific words. Keywords are written on the same page below the abstract.
5. Paper should be organized under suitable headings. Research article should follow Introduction, Methods, Results, Discussion and followed by acknowledgement and references. The literature review, in general, should be organized as introduction, text, closing and references; with content of the text should be relevant to the topic. Case report should be organized as follows: introduction, background, the case, discussion, conclusion and references.
6. Paper should be written using the correct Bahasa based on general guidlines spelling of enhanced Bahasa. Used the term of Bahasa as much as possible according to the general guidlines for the established of the term. The abbreviations used in the paper is an acronym which is standard
7. Tables should be numbered consecutively and provided with a brief title. Explanation and

unfamiliar abbreviations on the table should be written as footnotes. If table is copied from other published paper; it should be explained as "copied from" (names of authors and number in the references), and had written permission from the publisher. The number of table and picture should not exceed 6 pieces.

8. Graphics should be made professionally, photographed with sharp and clear printing on the glossy paper, black and white. If the pictures/ graph/illustration have been previously published, it should be written "copied from" (names of authors and references/ number in the list of references), accompanied with written permission from the publisher. Graphics should be explained in the back regarding number of the pictures in accordance with the text, name/title of the picture, names of authors. The number of table and picture should not exceed 6 pieces.
9. References.
   The number of references should not exceed 40. References should be taken from publications within the last 10 years. References of the Journal Respirology Indonesia should be included on-topic written.
10. References should follow the Vancouver style, numbered consecutively in the order of their appearance in the text. References numbers in the text are written in details as references, written as superscript, after punctuation marks (period, comma, etc.). In references, list all names of authors, except if more than six persons, write as follows: name of the first six, followed by et al. Avoid using references as abstract or personal communication. If using references that is still in the process of publication, add "in press". Principally, references should be followed the International Committee of Medical Journal Editors, that is Vancouver style, that was revised in 1997, and could be written in British medical Journal vol. 314, 5th January 1997.

The examples of references :

Book

Winn WC, Allen SD, Janda WM, Koneman EW, Procop GW, Schreckenberger PC, et al. Koneman's color atlas and textbook of diagnostic microbiology. 5th eds. Philadelphia: A Wolters Kluwer Company; 2006. p.1065-92.

Book with editor

Hopewell PC. Tuberculosis and other mycobacterial disease. In: Murray JF, Mason RJ, Broaddus VC, Nadel JA, editors. Textbook of respiratory medicine. 4 th edition. New York: WB Saunders Company; 2005.p.979-1043.

Journal

Edginton ME, Rakgokong L, Verver S, Madhi SA, Koornhof HJ, Wong ML, et al. Tuberculosis culture testing at a tertiary care hospital: options for improved management and use for treatment decisions. Int J Tuberc Lung Dis. 2008;12:786-91.

Thesis

Rassuna V. Pengamatan hasil akhir pengobatan tuberkulosis paru BTA negatif kasus baru di RS Persahabatan. Thesis Departemen Pulmonologi dan Ilmu Kedokteran Respirasi FKUI. Jakarta; 2008.

Organization resources

World Health Organization. Global Tuberculosis Control 2009 : epidemiology strategy financing. Geneva : WHO Press; 2009.p.11-32.

Perhimpunan Dokter Paru Indonesia. Tuberkulosis Pedoman diagnosis dan penatalaksanaan di Indonesia. Jakarta : Indah Offset Citra Grafika; 2006.p.1-8.

Electronic resources

The Highland Council. The Learning Environment. [Online].2010 [Cited 2011 November 28]. Available from:http://www.highlandschoolsvirtualib.org.uk/ltt/inclusive_enjoyable/environment.htm.

Sack K. With Medicaid cuts, doctors and patients drop out. The New York Times [Online]. 2010 Mar 16 [cited 2010 Mar 16]; Health:A1. Available from: http://www.nytimes.com/2010/03/16/health/policy/16medicaid.html?ref=health.

PUBLISHING AGREEMENT

We, the undersigned below:

Name :

Institution :

Mailing Address :

Number Phone :

Email :

We GIVE/DID NOT GIVE* full approval to the Jurnal Respirologi Indonesia to publish our article and the tools contained therein (if needed) entitled:

.....
.....
.....

We provide a statement:

1. We have compiled this article without any act of plagiarism and all sources, both quoted and referenced, have been properly stated.
2. The material in this article has never been published before and is not in the process of being published in other scientific journals.
3. We have the rights to the article and have never given the copyright of the article to anyone
4. We permit the Jurnal Respirologi Indonesia for all rights to production, distribution, reuse, and inclusion of part or all of the articles, including recompilation or stand-alone in any form of media now or in the future, including all electronic and digital media, under protection. applicable laws in the Republic of Indonesia and foreign countries and to authorize other parties to use the article properly. This authorization will become the property of the Jurnal Respirologi Indonesia as of the date of receipt of the article for publication.
5. we sign and accept the responsibility to provide this article's **Copyright** and **Non-exclusive Royalty-Free Right** to the Jurnal Respirologi Indonesia.
6. The article is free from plagiarism and is not the result of other people's work as evidenced by TurnItIn check results below 20%.
7. Willing to pay a publication fee of Rp. 1.000.000,00 or US$ 75,00

Place, Date
First Author/Corresponding Author,

(Name, signature)

*Select one

JURNAL
RESPIROLOGI
INDONESIA

Majalah Resmi Perhimpunan Dokter Paru Indonesia
Official Journal of The Indonesian Society of Respirology

VOLUME 43, NUMBER 3, July 2023

TABLE OF CONTENT

Original Article

Case Report

Original Article

Association of The Vaccination Status of Health Workers of COVID-19 Survivors with The Outcomes of Treatment of COVID-19 at General Hospital In Padang City

Kornelis Aribowo, Masrul Basyar, Yessy Susanty Sabri

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Dr. M. Djamil Padang General Hospital, Padang, Indonesia

Abstract

Background: Health workers are on the front lines of treating and fighting the COVID-19 pandemic. Health workers face COVID-19 patients at work. Health workers are at increased risk of infection if they are not properly protected. Increased risk for health workers can be caused by contact with patients without personal protective equipment (PPE) and surfaces contaminated with the virus. Infected health workers can infect other people around them and will increase the workload of other health workers. One of the efforts to reduce the risk of transmission to health workers is vaccination. Vaccines against COVID-19 are considered very important to prevent and control COVID-19. The aim is to determine the relationship between the COVID-19 vaccine status and the outcomes of healthcare workers treated for confirmed COVID-19 at hospitals throughout Padang.

Methods: This observational study was conducted using a retrospective cohort method. The study was conducted from August 2021 to May 2022 in hospitals across Padang by completing a questionnaire in the form of a Google form link.

Results: Vaccination status of health workers who survived COVID-19 who were treated at Padang City General Hospital (66.97%) were not vaccinated, aged 26–35 years (57.80%), female (80.73%), worked as paramedics (63, 55%), symptom onset 3 to 7 days (44.95%), number of symptoms 3 (55.96%), most fever (24.68%), number of comorbid 1 to 2 (66.06%), obesity (66.67%), length of stay <21 days (84.40%), and mild clinical (55.96%) and recovered (92.66%). The highest degree of COVID-19 severity for health workers who were not vaccinated was moderate clinical, 42 samples (57.53%), and vaccinated, predominantly mild clinical, 34 samples (94.44%). The duration of stay of health workers vaccinated was higher than that who were not vaccinated (97.22% vs. 78.08%).

Conclusion: The vaccination status of health workers who have survived COVID-19 relates to a clinical degree, length of stay, and outpatient treatment.

Keywords: COVID-19, health workers, outcome hospitalization, vaccination

Corresponding Author:
Kornelis Aribowo | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Dr. M. Djamil Padang General Hospital, Padang, Indonesia | dokterkornelis@gmail.com

Submitted: June 6th, 2022
Accepted: February 6th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 158–66
https://doi.org/10.36497/jri.v43i3.351

INTRODUCTION

Health workers are the front-line medical personnel to treat and fight the COVID-19 pandemic.[1] Itodo's research states an increased risk of SARS-CoV-2 infection for health workers who treat COVID-19 compared to the general public.[2] This potential is because health workers work in long-term exposures. Failure to apply for adequate personal protection, PPE either does not meet standards or is reused, and lack of training, infection control, monitoring, prevention, and control mechanisms.[3]

The COVID-19 vaccine helps protect the body from falling ill due to COVID-19 by generating or stimulating specific immunity in the body. This process causes the vaccine to reduce the viral load in the infection process, thereby suppressing further transmission. This reduction in viral load implies a lower transmission potential, contributing to the vaccine's effect on virus spread.[4]

Bernal's study found that there were differences between vaccinated and unvaccinated patients. Of those who were not vaccinated, 543 (56%) had symptoms of COVID-19, and 140 (14%) were asymptomatic on or 14 days before the date of a positive PCR test, compared with 29 (36%) with typical COVID-19 symptoms and 15 (19%) were asymptomatic in the vaccinated group.[5]

The Redmon study found that 80 (5.7%) of 1.408 unvaccinated patients had COVID-19, and 12 (0.3%) of 4.222 were vaccinated. Patients who were vaccinated had mild symptoms, and none required

hospitalization.[6] Baz's research found that from 7240 COVID-19 patients, there were 260 (18.8%) people had been vaccinated, but only 161 people (11.7%) had symptoms and treated only 11 people (0.8%). These data show that vaccination can reduce the symptoms and treatment of COVID-19.[7] Hyams research stated that by vaccinating the older patients, >70 years of age to 180 COVID-19 patients, there was a decrease in care from 72% to 57% after the second vaccination and more treatment shorter than unvaccinated.[8]

METHODS

This study is an observational analytic study with a retrospective cohort method. The research was conducted in hospitals throughout the city of Padang, namely Regional General Hospital Dr. M. Djamil, Padang City, Andalas University Hospital, Semen Padang Hospital, BMC Hospital, Hermina Hospital, Yos Sudarso Hospital, Ibnu Sina Hospital, Reksowidiryo Army Hospital, Bhayangkara Hospital, Naili DBS Hospital, Siliguri Hospital, RS Aisyiyah. The research was carried out from August 2021 to May 2022.

According to the Law of the Republic of Indonesia Number 36 of 2014, health workers are every person who devotes himself to the health sector and has the knowledge and skills through education in the health sector which, for certain types, require the authority to carry out health efforts. They are broadly divided into a) medical personnel: specialist doctors, general practitioners, dentists, and specialist medical education programs; b) paramedics: nurses and midwives; c) supporting personnel: laboratory analysts, laboratory assistants, pharmacists, pharmacist assistants, radiographers, nutritionists, nutritionists and dietitians, electromedical, medical laboratory technologists, medical physicists, radiotherapists and prosthetic orthotics, medical recorders and health information, cardiovascular techniques, service technicians blood, optometrist, dental technician, anesthesiologist, dental and oral therapist, and audiologist, physiotherapist, occupational therapist, and speech therapist. Vaccination status for COVID-19 consists of a) not vaccinated: never been vaccinated until infected with COVID-19; and b) vaccinated: fully vaccinated against COVID-19 twice until infected with COVID-19.

The sampling technique of the inclusion criteria in this study was health workers who were confirmed to have COVID-19 from the results of the *Reverse Transcriptase – Polymerase Chain Reaction* (RT-PCR), hospitalized for COVID-19, willing to participate in this study and filled out the questionnaire. The exclusion criteria for this research is an incomplete *Google form*. The characteristics of the data are presented in tabular form and processed statistically.

RESULTS

The total number of survivors of COVID-19 health workers in COVID-19 treatment based on vaccine status consisted of 36 health workers who had been vaccinated (33.03%) and 73 health workers who were not vaccinated (66.97%), as shown in Figure 1.

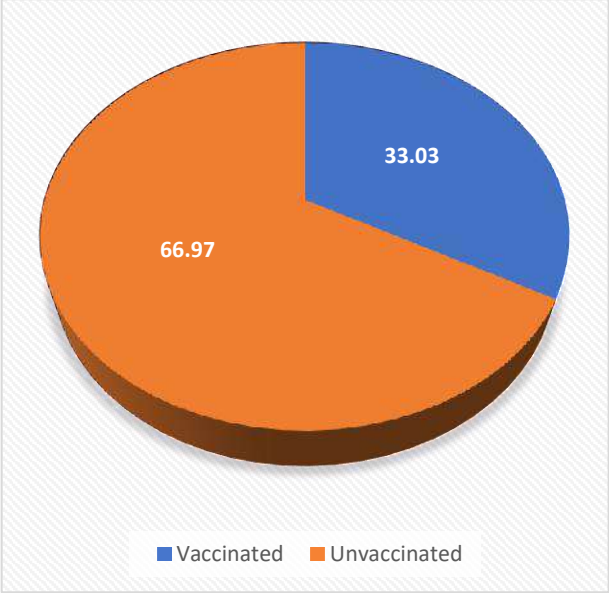

Figure 1. COVID-19 vaccine status in hospitalized health workers

Health workers suffering from COVID-19 treated at hospitals throughout the city of Padang were generally 26-35 years old (57.80%), followed by the 36–45 age group (19.27%). Females (80.73%) were treated more than males (19.27%).

Table 1. Characteristics of Health Workers suffering from COVID-19 being treated at General Hospital throughout the City of Padang

Characteristic	Total subject (N=109)	Vaccinated (N=36)	Unvaccinated (N=73)	*P*
Aged (years)				
17–25	16 (14.68)	8	8	
26–35	63 (57.80)	19	44	
36–45	21 (19.27)	6	15	0.399[b]
46–55	6 (5.50)	2	4	
>56	3 (2.75)	1	2	
Gender				
Male	21 (19.27)	6	15	0.629[a]
Female	88 (80.73)	30	58	
Occupation				
Medical personnel	25 (23.36)	13	14	
Paramedic	68 (63.55)	21	47	0.414[b]
Supporting Personnel	8 (7.48)	2	6	
Administration staff	6 (5.61)	0	6	
The onset of Symptoms (days)				
<3	31 (28.44)	14	17	
3–7	49 (44.95)	14	35	0.0001[a]
>7	29 (26.61)	8	21	
Symptoms				
Fever	76 (24.68)	29	47	0.084[a]
Cough	51 (16.56)	19	32	0.379[a]
Breathlessness	27 (8.77)	8	19	0.665[a]
Gastrointestinal disorders	23 (7.47)	5	18	0.195[a]
Anosmia	49 (15.90)	20	29	0.118[a]
Ageusia	18 (5.84)	12	6	0.001[a]
Headache	64 (20.78)	26	38	0.044 [a]
Number of symptoms				
No symptoms	13 (11.93)	2	11	
1-2	35 (32.11)	8	27	0.009[b]
≥3	61 (55.96)	26	35	
Number of comorbidities				
No comorbid	36 (33.03)	15	21	
1-2	72 (66.06)	21	51	0.546[b]
≥3	1 (0.91)	0	1	
Comorbidities				
Hypertension	10 (9.80)	2	8	0.016[a]
Diabetes mellitus	2 (1.96)	0	2	0.316[a]
Cerebrovascular	2 (1.96)	1	1	0.153[a]
Cardiovascular	7 (6.86)	2	5	0.734[a]
Kidney illness	2 (1.96)	1	1	0.153[a]
Asthma/COPD	9 (8.83)	3	6	0.363[a]
Obesity	68 (66.67)	18	50	0.544[a]
Autoimmune	2 (1.96)	0	2	0.316[a]

Note: [a]Chi-Square test; [b]Pearson chi-square test; *P*<0.05 significant

Table 2. The Relationship between COVID-19 Vaccination Status and the Clinical Degree of Padang City Health Workers

Vaccination Status	Clinical Degree			*P*
	Mild (N=61)	Moderate (N=44)	Severe (N=4)	
Unvaccinated	27 (36.99 %)	42 (57.53 %)	4 (5.48 %)	0.0001
Vaccinated	34 (94.44 %)	2 (5.56 %)	0 (0 %)	

The most occupations are paramedics (63.55%), followed by medical personnel (23.36%). The onset of symptoms when infected was highest at a distance of 3 to 7 days (45%), followed by <3 days (28.44%). The duration for confirmed COVID-19 health workers vaccinated and treated at the general

hospital throughout Padang is more than 28 days after vaccination (86.11%). The most common symptom was fever (24.68%) and followed by headache (20.8%), with the most complaints of three symptoms (55.96%). The highest number of comorbidities is 1 to 2 types (66.06%), with the most comorbidities in health workers being treated, namely obesity (66.67%), as shown in Table 1.

Health workers suffering from COVID-19 who were not vaccinated with mild clinical grade followed by moderate clinical and severe clinical-critical were different from those vaccinated. Health workers who had been vaccinated did not find any clinical severity critical. The clinical degree of mild after vaccination was 94.44%, and moderate clinical was 5.56%. Health workers confirmed to have COVID-19 after vaccination was found to be mainly at a mild clinical degree, while the highest number were not vaccinated at a moderate clinical degree, as shown in Table 2. Statistic analysis shows a significant relationship with the Pearson chi-square test between the status of the COVID-19 vaccination and the clinical degree of health workers suffering from COVID-19 treated at hospitals throughout Padang, with *P*=0.0001.

Health workers suffering from COVID-19 who were neither vaccinated nor vaccinated were the most in the length of stay <21 days (78.08% and 97.22%). Based on the table, the percentage of the length of stay for health workers suffering from COVID-19 who were treated at hospitals throughout the city of Padang for those who were not vaccinated was higher than those who were vaccinated (21.92% vs. 2.78%). The relationship between vaccine status and length of stay for health workers suffering from COVID-19 treated at hospitals throughout the city of Padang in a statistical test showed *P*=0.021 (*P*<0.05), which showed a significant relationship. The length of stay for COVID-19 in those vaccinated for <21 days was greater than that in those vaccinated because the clinical symptoms in health workers who were vaccinated mainly were mild clinical (94.44%), as shown in Table 3.

Health workers suffering from COVID-19 who were not vaccinated and vaccinated against outpatient healthcare treatment recovered (94.52% and 88.89%), followed by recovery with residual symptoms (5.48% and 11.11%). The relationship between vaccination status and the outpatient healthcare workers suffering from COVID-19 who were treated at hospitals throughout the city of Padang with a statistical test, the results obtained *P*=0.289 so that there was no significant relationship between the status of the COVID-19 vaccination and the outpatient of COVID-19 treatment in health workers who are being treated at hospitals throughout the city of Padang.

Table 3. The Relationship between the Status of the COVID-19 Vaccination and the Length of Hospitalization of Padang City Health Workers

Vaccination Status	Duration of Treatment		*P*
	<21 days (N = 92)	≥21 days (N=17)	
Unvaccinated	57 (78.08 %)	16 (21.92%)	0.021
Vaccinated	35 (97.22 %)	1 (2.78 %)	

Table 4. Relationship between COVID-19 Vaccination Status and Outpatient of COVID-19 Treatment at Padang City Health Workers

Vaccination Status	End of Treatment Status		*P*
	Healed (N=101)	Recover residual symptoms (N=8)	
Unvaccinated	69 (94.52 %)	4 (5.48 %)	0.289
Vaccinated	32 (88.89 %)	4 (11.11 %)	

DISCUSSION

This study shows that most COVID-19 health workers who are hospitalized are in the 26–35 year age group (57.80%), followed by the 36–45 year age group (19.27%). This study's results align with those of Soebandrio et al, who got the most age at <39 years.[9] Nguyen's study is slightly different from this study. Most health workers are aged 35–44 years (23.30%), followed by 25–34 years (21.95%).[2] The majority of this study was at the age of 26-35 because, in that age range, the active, productive age group worked in the COVID-19 isolation room, causing increased exposure to the SARS-COV-2 virus.

The highest gender in this study was female (80.73%). This result is the same as Antonelli's study, primarily women (62.50%) and Nguyen's (81%).[2,10] Different results were obtained in Hussen's study of health workers in Ethiopia, with 55.30% male.[11] This

study was mostly female because most health workers in Padang City were female, and women were more prone to suffering from stress fatigue, depression, and anxiety, usually related to longer shifts, poor working conditions, and lack of recognition, thereby lowering immunity and increasing the risk of COVID-19 infection.[11]

Most of this research is paramedics (62.40%) followed by medical personnel (24.80%). This result aligns with Bergwerk's study, where the highest number of paramedics (46%) and Manglano (33.90%).[12,13] This result differs from Soebandrio's study in Jakarta, where the highest number of medical personnel (48.40%) was followed by paramedics (44.20%).[9] Paramedics also dominated the population in this study, so the incidence of paramedics was more than medical personnel. In theory, high exposure is for paramedics and medical personnel.

This study showed the most symptom onset before confirmed COVID-19 at 3 to 7 days (44.95%) followed by <3 days (28.44%) and above seven days (26.61%) and statistically significant (*P*=0.0001). The incubation period for COVID-19 is the time interval between when a person is infected and the likelihood of developing COVID-19 disease or symptoms in a confirmed case. The time between the occurrence of exposure to the onset of symptoms, called the incubation period, usually occurs within two to 14 days.

This study found that the distance between confirmed COVID-19 with the second vaccination was more than 28 days (86.11%), followed by 15–27 days (8.33%) and 14 days (5.56%). This result is in line with the study of Bergwerk et al in the breakthrough case of COVID-19 in health workers, where the average interval from the second vaccination dose to the detection of SARS-CoV-2 was 39 days.[12] Different results from the Cucunawangsih study in Indonesia, obtained from 1.040 health workers who had received two doses of the COVID-19 vaccine, 13 (1.25%) tested positive for SARS-CoV-2 RNA with a mean between 2 and 11 days (median five days) after the second vaccination.[14] This study was mainly in >28 days, where according to the theory of SARS-CoV2, antibodies will decrease over time.

Most of the clinical symptoms in this study were fever (24.68%), followed by headache (20.78%), and cough (16.56%). The same study in Loon's study in Belgium on COVID-19 health workers, most of which was cough (82%), headache (78%), and fever (76%).[15] It is different in Magnavita's study, where the most common symptoms of infected COVID-19 health workers are muscle pain (52.40%), fatigue (47.60%), anosmia (42.70%) and dysgeusia (37.80%).[16] Symptoms of fever, headache, and cough in this study were the main complaints of patients to be treated.

Most health workers in this study had three clinical symptoms (55.96%), followed by one to two clinical symptoms (32.11%) and no symptoms (11.93%). Vahey's study in 128 treated patients found that the most symptoms were three, with the most being cough, but symptoms of vomiting, dyspnea, changes in mental status, dehydration, and shortness of breath were significantly associated with hospitalization.[17]

In contrast, rhinorrhea, headache, sore throat, and anosmia or ageusia were significantly associated with non-hospitalization.[17] The Magnavita study found that health workers affected by COVID-19 were most affected by two symptoms followed by three symptoms.[16] The number of these symptoms will be directly proportional and significantly to the severity of the disease.

The most comorbidities in this study were obesity (66.67%) followed by hypertension (9.80%) and asthma/COPD (8.82%). This study aligns with the Kambhampati study with the most obesity (72.50%).[18] This slightly differs from Bennasrallah's (2020) study on 265 COVID-19 patients. It was found that obesity was the third most comorbid (15.40%) after diabetes (16,80%) and hypertension (15.60%).[19] Healthcare workers with obesity are associated with reduced lung oxygen and low-grade inflammation associated with obesity, such as impaired secretion of abnormal cytokines, adipokines, and interferon consequences in the

immune response.[19]

Obese patients, also there will be an increase in acute phase reactants that are related to the severity of inflammation, namely CRP, serum ferritin, D-dimer, Erythrocyte sedimentation rate (ESR), and LDH.[20] Obesity is associated with an increased risk of diabetes mellitus, hypertension, and cardiovascular disease. The greater the number of co-morbidities in obese patients, the greater the severity of COVID-19. The respiratory system is also altered in obesity. Changes in the respiratory mechanism, increased airway resistance, and decreased lung volume can impair gas exchange.[15]

This study found that the group with comorbidities 1 to 2 was the most prominent (66.06%). This result is in line with the study by Giannouchous et al, who found that in patients treated based on the highest number of comorbidities, one comorbid (26.85%) was followed by two comorbid (12.65%).[20] The same result also occurred in Richardson's study, most of which had more than one comorbid (88%) followed by one comorbid (6.30%) and no comorbid (6.10%).[21] The number of comorbidities has a close relationship with poor outcomes because multiple comorbidities will contribute to the disease's complexity, impacting disease progression.[20]

Health workers who did not vaccinate were the highest at the moderate clinical degree at 57.53% and vaccinated at 94.44%. Mild clinical degrees in the unvaccinated and vaccinated were 36.99% and 94.44%, respectively. Moderate clinical degrees in the unvaccinated and vaccinated were 57.53% and 5.56%, respectively. Critical severity (2.7%) was only found in health workers who were not vaccinated. This study found a significant relationship between the status of the COVID-19 vaccination and the clinical degree of health workers treated at the Padang City Hospital (*P*=0.0001). In the Tenforde et al study, mortality within 28 days was related to vaccination status (8.6% not vaccinated vs. 6.3% vaccinated).[22]

Some unvaccinated individuals with COVID-19 had a longer duration of illness.[22] The World Health Organization's Clinical Progression Scale states that the highest severity was significantly lower in the breakthrough case than in the unvaccinated. COVID-19 patients vaccinated have the highest degree of severity, namely mild 14 patients (42.4%) followed by severe nine patients (30.3%).[23] Ramakrishnan's study of 3301 unvaccinated patients found 291 patients (8.8%) required an ICU, and this was significantly less (*P*=0.03) than among the vaccinated 31 of 519 patients (6%).[24]

Patients who were not vaccinated were more likely to be hospitalized (2.8%), admitted to the ICU (0.5%), and required intubation for mechanical ventilation (0.2%); these results were less common in people who were fully vaccinated with a booster (0.7%, 0.08%, and 0.03%, respectively) and people who were utterly vaccinated without a booster (1.0%, 0. 12%, and 0.05%) (*P*<0.001). Death was also more likely among people who were not vaccinated (0.3%) than among those who were fully vaccinated with a booster (0.07%) or without (0.08%) (*P*<0.001).[23]

In this study, vaccinated health workers, the length of stay for <21 days was 35 people (97.22%), and >21 days was one person (2.78%). Unvaccinated health workers also had a more extended stay of <21 days than a more prolonged stay of >21 days (78.08% vs 21.92%). Statistical tests obtained significant results (*P*=0.02). This study found that the length of stay <21 days was highest in those vaccinated because health workers were mostly in mild clinical cases. The results obtained in Tenforde's study for COVID-19 treatment, 1197 patients who received hospitalization (<28 days) were higher in patients who were vaccinated than those who were not vaccinated (88% vs. 77.20%) and statistically significant (*P*=0.003).[22]

Singh's study found a statistically significant value for the length of stay for COVID-19 on vaccinated and unvaccinated (10 days vs. 12 days; *P*=0.034).[23] Vaccination can protect against the SARS-CoV2 virus, is associated with length of stay for COVID-19, and provides a protective barrier against re-infection.[25] Some individuals who are not vaccinated against COVID-19 have a longer duration

of illness.[10] Other factors contributing to the length of hospitalization in addition to vaccination are comorbid. Jang's research in Korea found that the more comorbidities, the longer the length of stay.[26]

Health workers suffering from COVID-19 who were not vaccinated and vaccinated against the final status of COVID-19 treatment recovered (94.52% and 88.89%), followed by recovery with residual symptoms (5.48% and 11.11%). The statistical test found that there was no significant relationship with the *P=0.*289. The results were the same in Singh's study, where the percentage of cure was 81.80% for those who were vaccinated and 71.80% for those who were not vaccinated, but the mortality rate was higher for those who were not vaccinated (28.20% vs. 18.20%).[23]

Research by Johnson et al conducted on 22.305 COVID-19 patients based on vaccination status, the mortality rate in unvaccinated patients was 7.8% (16.527 patients), and the mortality rate was lower in fully vaccinated patients by 0.6% (5.493 patients).[27] In a multivariable analysis, vaccination reduced mortality by 60 days (*P*<0.001).[24] The Washington State Department of Health found higher mortality at age 65 based on vaccination status.[28]

LIMITATION

This study did not include the last time they were vaccinated when they tested positive for COVID-19 because the effectiveness of vaccinations can decrease over time.

CONCLUSION

The vaccination status of health workers who survived COVID-19 who were treated at the Padang City Hospital consisted of 66.97% unvaccinated and 33.03% vaccinated. Characteristics of health workers who survived COVID-19 aged 26–35 years, female, working as a paramedic, onset of symptoms 3 to 7 days, number of symptoms 3, highest fever, number of co-morbidities 1 to 2, obesity, length of stay <21 days, and clinical light. The vaccination status of health workers for COVID-19 survivors is related to the clinical degree and length of hospitalization. Vaccinated patients are not associated with post-COVID-19 survivor sequelae.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Lan FY, Filler R, Mathew S, Buley J, Iliaki E, Bruno-Murtha LA, et al. COVID-19 symptoms predictive of healthcare workers' SARS-CoV-2 PCR results. PLoS One. 2020;15(6):e0235460.
2. Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, et al. Risk of COVID-19 among front-line health-care workers and the general community: A prospective cohort study. Lancet Public Health. 2020;5(9):e475–83.
3. Itodo GE, Samson Enitan S, Oyekale AO, Agunsoye CJ, Asukwo UF, Enitan CB. COVID-19 among healthcare workers: Risk of exposure, impacts and biosafety measures - a review. ASJ: International Journal of Health, Safety and Environment (IJHSE). 2020;6(04):534–48.
4. Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, et al. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nat Med. 2021;27(5):790–2.
5. Bernal JL, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. BMJ. 2021;373:n1088.

6. Redmond SN, Jones LD, Sadri N, Schmotzer C, Navas ME, Zabarsky TF, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in vaccinated and unvaccinated healthcare personnel in a Veterans' Affairs healthcare system. Infect Control Hosp Epidemiol. 2022;43(9):1300–1.
7. Martínez-Baz I, Miqueleiz A, Casado I, Navascués A, Trobajo-Sanmartín C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Euro Surveill. 2021;26(21):2100438.
8. Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination in prevention of hospitalisations people aged at least 80 years: a test-negative, case-control study. Lancet Infect Dis. 2021; 21(11):1539-48
9. Soebandrio A, Kusumaningrum T, Yudhaputri FA, Oktavianthi S, Safari D, Malik SG, et al. COVID-19 prevalence among healthcare workers in Jakarta and neighbouring areas in Indonesia during early 2020 pandemic. Ann Med. 2021;53(1):1896–904.
10. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis. 2022;22(1):43–55.
11. Hussen H, Alemu ZA. Risk of COVID-19 infection and associated factors among healthcare workers: A cross-sectional study at Eka Kotebe Treatment Center in Ethiopia. Int J Gen Med. 2021;14:1763–72.
12. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers. New England Journal of Medicine. 2021;385(16):1474–84.
13. Díez-Manglano J, Solís-Marquínez MN, García AÁ, Alcalá-Rivera N, Riesco IM, Aseguinolaza MG, et al. Healthcare workers hospitalized due to COVID-19 have no higher risk of death than general population. Data from the Spanish SEMI-COVID-19 Registry. PLoS One. 2021;16(2):e0247422.
14. Cucunawangsih C, Wijaya RS, Lugito NPH, Suriapranata I. Post-vaccination cases of COVID-19 among healthcare workers at Siloam Teaching Hospital, Indonesia. Int J Infect Dis. 2021;107:268–70.
15. Van Loon N, Verbrugghe M, Cartuyvels R, Ramaekers D. Diagnosis of COVID-19 based on symptomatic analysis of hospital healthcare workers in Belgium: observational study in a Large Belgian Tertiary Care Center during early COVID-19 outbreak. J Occup Environ Med. 2021;63(1):27–31.
16. Magnavita N, Tripepi G, Di Prinzio RR. Symptoms in health care workers during the COVID-19 epidemic. A cross-sectional survey. Int J Environ Res Public Health. 2020;17(14):1–15.
17. Vahey GM, Marshall KE, McDonald E, Martin SW, Tate JE, Midgley CM, et al. Symptom profiles and progression in hospitalized and nonhospitalized patients with coronavirus disease, Colorado, USA, 2020. Emerg Infect Dis. 2021;27(2):385–95.
18. Kambhampati AK, O'Halloran AC, Whitaker M, Magill SS, Chea N, Chai SJ, et al. COVID-19-associated hospitalizations among health care personnel - COVID-NET, 13 States, March 1-May 31, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(43):1576–83.
19. Bennasrallah C, Zemni I, Dhouib W, Sriha H, Mezhoud N, Bouslama S, et al. Factors associated with a prolonged negative conversion of viral RNA in patients with COVID-19. International Journal of Infectious Diseases. 2021;105:463–9.
20. Giannouchos T V., Sussman RA, Mier JM, Poulas K, Farsalinos K. Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory–confirmed COVID-19 cases. European Respiratory Journal. 2021;57(3):2002144.

21. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052–9.
22. Tenforde MW, Self WH, Gaglani M, Ginde AA, Douin DJ, Talbot HK, et al. Effectiveness of mRNA vaccination in preventing COVID-19–associated invasive mechanical ventilation and death — United States, March 2021–January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(12):459–65.
23. Singh C, Naik BN, Pandey S, Biswas B, Pati BK, Verma M, et al. Effectiveness of COVID-19 vaccine in preventing infection and disease severity: a case-control study from an Eastern State of India. Epidemiol Infect. 2021;149:e224–e224.
24. Ramakrishnan M, Subbarayan P. Impact of vaccination in reducing hospital expenses, mortality and average length of stay among COVID-19 patients – A retrospective cohort study from India. medRxiv. 2021;
25. León TM, Dorabawila V, Nelson L, Lutterloh E, Bauer UE, Backenson B. COVID-19 Cases and Hospitalizations by COVID-19 Vaccination Status and Previous COVID-19 Diagnosis — California and New York , May – November 2021. MMWR Morb Mortal Wkly Rep. 2022;71(4):125–31.
26. Jang SY, Seon JY, Yoon SJ, Park SY, Lee SH, Oh IH. Comorbidities and factors determining medical expenses and length of stay for admitted COVID-19 patients in Korea. Risk Manag Healthc Policy. 2021;14:2021–33.
27. Johnson AG, Amin AB, Ali AR, Hoots B, Cadwell BL, Arora S, et al. COVID-19 incidence and death rates among unvaccinated and fully vaccinated adults with and without booster doses during periods of delta and omicron variant emergence - 25 U.S. Jurisdictions, April 4-December 25, 2021. MMWR Morb Mortal Wkly Rep. 2022;71(4):132–8.
28. Washington State Department of Health. COVID-19 hospitalizations and deaths by vaccination status in Washington State. Washington; 2023.

Original Article

Magnesium and Phosphate Ion Levels in Mechanically Ventilated Patients Treated at Persahabatan Hospital's Intensive Care Unit (ICU) and Respiratory Intensive Care Unit (RICU) in 2018

Filemon Suryawan Handjaja[1], Menaldi Rasmin[1], Prasenohadi[1], Ernita Akmal[2]

[1] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan Hospital, Jakarta, Indonesia
[2]Anesthesiology Functional Medical Staff, Intensive Care Installation - Persahabatan Hospital, Jakarta, Indonesia

Abstract

Background: History shows that respiratory system has a long and complicated arrangement so that many factors can affect a human's ability to breathe. Some electrolytes often considered as most important are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and chloride (Cl^-). Other than that, magnesium (Mg^{2+}) and phosphate (PO_4^{3-}) are also important in all processes, especially at the neuromuscular junction and in muscle cells as adenosine triphosphate (ATP). Some researchers have found that PO_4^{3-} affected patients' clinical condition and ventilator weaning success, although Mg^{2+} gave inconsistent results. Until now, there have not been any studies or data about the significance of Mg^{2+} and PO_4^{3-} in ventilator weaning in Indonesia.

Methods: This was a cross sectional study with total sampling. A vein blood sample was taken after ICU/RICU admission at Persahabatan Hospital. Blood sample was taken consecutively until it reached a minimum of 30 subjects (pilot study). All patients found with mechanical ventilation were included, except for patients with complicated procedure (e.g. avian influenza, multidrug-resistant tuberculosis). Blood sample was analyzed for Mg^{2+}, inorganic phosphate (Pi) and other additional tests. Failure in weaning was defined as reintubation within 48 hours after extubation or failure in the spontaneous breathing trial (SBT).

Results: Of the 31 subjects evaluated, there were 3 patients with weaning failure. The median Mg^{2+} value was 0.5 (0.5-2.6) in successfully weaned patients and 0.6 (0.6-2.7) in patients with weaning failure, lower than its normal value. The mean Pi value was 4.21±1.17 (normal value) in successfully weaned patients and 5.43±0.47 (high value) in patients with weaning failure. Further analysis found that no significant relation was found between weaning and patient's characteristics other than heart rate and Ca^{2+}, although it was not clear if there were some biases which could affect these results. Low Mg^{2+} value was observed in 23 subjects, no low Pi value was seen in all subjects, high Mg^{2+} value was found in 1 subject, high Pi value was observed in 11 subjects, and the rest was in the normal range.

Conclusion: The median Mg^{2+} value in both weaning groups (successful and failed) were below the normal limit at 0.5 (0.5-2.6) and 0.6 (0.6-2.7). Mean Pi value in the successful weaning group was 4.21±1.17 (within normal range), and the value in failed weaning group was 5.43±0.47 (above normal range).

Keywords: magnesium, mechanical ventilation, phosphate, weaning

Corresponding Author:
Filemon Suryawan Handjaja | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan Hospital, Jakarta, Indonesia | drfilemonsh@gmail.com

Submitted: December 10th, 2020
Accepted: February 27th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 167–76
https://doi.org/10.36497/jri.v43i3.456

INTRODUCTION

The respiratory system is one of the important mechanisms that support human life. This system has many pathways that must be passed from the central nervous system to the respiratory muscles as effectors in carrying out their functions. All of these pathways can be grouped into the neuro-respiratory system. Galen was a doctor from Greece who realized that enslaved people or animals that had trauma to the vertebrae below the neck could still breathe spontaneously. In contrast, breathing movements immediately disappeared in high-lying vertebral trauma (the neck area). Since then, the role of the central nervous system in controlling respiration has been understood.[1–3]

Control of the respiratory system by the central nervous system was first described by a neurologist named Whytt. He realized that breathing could be controlled at will, even though it was involuntary. Lorry, in 1760 postulated that areas of the brainstem control regular breathing. This was concluded from the persistence of respiratory movements in rabbits after the cerebrum and cerebellum of the rabbit were

removed. A French scientist named Francois-Frank discovered the cortical (voluntary) breathing control center when he saw changes in breathing patterns in experimental animals that were given stimulation in their cortex.[1,4]

This history shows that the respiratory system has a long and complicated arrangement. Many factors can affect human breathing ability. There have been no studies directly on human muscles in vitro to date, but many studies have been conducted on mammals that can be compared. Some important ions that are often considered are sodium (Na+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl-). Magnesium (Mg^{2+}) and phosphate (PO_4^{3-}) are also important in all the processes, especially in the muscle-nerve junction and the muscle itself.[5–8]

Several researchers, such as Dhingra et al, Fiaccadori et al, Moe, Aubier et al, Gravelyn et al, and Zhao et al, showed the importance of Mg^{2+} and PO_4^{3-} levels on respiratory muscle strength and successful weaning in patients treated in Intensive Care Unit (ICU).[9–14] Dhingra et al and Fiaccadori et al gave conflicting results regarding the importance of Mg^{2+} levels to the clinical condition of patients.[9,10]

Other researchers provided similar results regarding the importance of PO_4^{3-} levels to the clinical condition of patients and the success rate of weaning from invasive mechanical ventilation.[11–14] Until now, no similar studies have been conducted in Indonesia with patient characteristics that differ from previous studies. This study aims to find basic data on Mg^{2+}, PO_4^{3-} level profiles, physiological profiles, and other pathological profiles in patients with invasive mechanical ventilation.

This study aimed to determine the physiological and pathological profiles of ICU and RICU patients with invasive mechanical ventilation at Persahabatan General Hospital after the first weaning and after successful re-weaning.

METHODS

The study was conducted with a cross-sectional design in patients treated in the ICU and RICU of Persahabatan General Hospital who used invasive mechanical ventilation. The study population was all ICU and RICU care patients at Persahabatan Hospital from January 1st, 2018, to December 31st, 2018.

The study sample was all ICU and RICU patients at Persahabatan Hospital who used invasive mechanical ventilation from January 1st, 2018, to October 30th, 2018, and underwent the weaning procedure at least once during the treatment period. The minimum number of samples in the pilot study, according to Johanson et al, was 30 subjects, but as many as possible were taken during the sampling period.[15]

All patients admitted to ICU and RICU were going to be examined according to the APACHE II score plus other tests as contained. All therapy and patient intake were recorded and included in the study status. Subsequent checks were carried out after the first weaning and subsequent weaning if the first weaning failed and the last weaning was successful. If the second weaning and so on were not successful, there was no need to examine the study, according to the status of the study.

All blood specimens were taken and put into blood tubes without heparin. The specimen was then centrifuged for 30 minutes so that the serum could be examined. Electrolyte levels, especially Mg^{2+}, were checked using pHOx Ultra by flowing the serum through an isoelectric membrane. The value was then calculated based on the movement of ions across the membrane. Pi levels were checked using the phosphomolybdate method and then exposed to 340 nm light, and the turbidity was calculated to determine the Pi value.

The inclusion criteria in this study were all lung patients treated at the ICU and RICU at Persahabatan Hospital who used invasive mechanical ventilation and underwent a weaning procedure at least once during the treatment period. Exclusion criteria in this study were patients aged less than 12 years to equalize the normal value of vital signs, patients with infectious infections that complicated the procedure (e.g., avian influenza), and the patient's family refused to collect patient data.

RESULTS

The total subjects included in the study were 32 patients, but 1 patient was excluded from the analysis because there were no calcium, magnesium, or phosphorus examination results. A total of 28 subjects successfully underwent weaning from invasive mechanical ventilation, and the remaining 3 subjects failed to undergo weaning.

The characteristics of the study subjects were divided based on sex, age, BMI, BMI classification, Mean Arterial Pressure (MAP), MAP classification, pulse frequency, respiratory rate, O_2 saturation (pulse oximetry), hemoglobin, hematocrit, platelets, leukocytes, urea, creatinine, sodium, potassium, chloride, calcium, magnesium, phosphorus, APACHE II score, and disease classification (Table 1).

Table 1. Characteristics of study patients

Characteristics	Value on weaning	
	Succeed	Fail
Gender		
Men	16	1
Women	12	2
Age	45.07±16.42	46±14.11
BMI	23.12±4.32	23.11±2.7
BMI Classification		
Normal	14	3
Abnormal	14	0
MAP	99.89±21.51	77±18.66
MAP Classification		
Low	1	1
Normal	27	2
Pulse frequency	95.9±27.85	133±31.77
Breathing frequency	17.5 (12-31)	23±7
O_2 pulse saturation	100 (90-100)	100
Hemoglobin	11.66±2.05	9.53±1.56
Hematocrit	34.47±6.05	28.77±5.72
Platelets (thousand)	233.5 (3-1.165)	408±236.32
Leukocytes	15.935 (7.470-48.830)	24.240±9.530.11
Urea	27 (13-244)	62.33±76.12
Creatinine	0.75 (0.4-8.6)	1.47±1.51
Sodium	135.96±4.27	136±8.19
Potassium	3.85 (2.8-7.4)	5.06±1.27
Chloride	103.51±5.96	104.67±8.02
Calcium	1.23±0.07	1.33±0.1
Magnesium	0.5 (0.5-2.6)	0.6 (0.6-2.7)
Phosphor	4.21±1.17	5.43±0.47
APACHE II score		
A score	8 (0-25)	4 (4-24)
B score	2 (0-6)	1.67±1.53
C score	0 (0-5)	0 (0-5)
Total Score	11.5 (2-36)	14±11.36
Disease Classification		
Surgery		
Abdomen	11	1
ENT	4	0
Thorax	2	1
Nerve	3	0
Heart	1	0
Bone	1	0
Non-Surgical		
Lung infection	5	1
Abdominal malignancy	1	0

A total of 16 of the 31 patients who were successfully weaned were male, and 12 \were female, while 1 male patient and 2 other female patients failed to wean. The mean age, BMI, sodium, and chloride in the successful weaning group were 45.07±16.42, 23.12±4.32, 135.96±4.27, and 103.51±5.96. These values were similar to those of the failed weaning group, namely 23.11±2.7, 23.11±2.7, 136±8.19, and 104.67±8.02. A total of 3 patients failed to wean and died (Table 1).

Value of MAP were normal in 2 patients and low (<65 mmHg) in 1 patient. The pulse rate was normal in 1 patient and increased (tachycardic) in 2 patients. Tachypnea was found in 1 patient, and normal respiratory rate was observed in 2 patients. A total of 2 of the 3 patients experienced hyponatremia and hypomagnesemia. K^+ and Ca^{2+} values were normal in 2 of 3 patients. Hyperkalemia, hyperchloremia, hypercalcemia, and hypermagnesemia were present in 1 out of 3 patients who failed to wean. Hyperphosphatemia was found in all three patients. No hypophosphatemia was found in all patients who failed to wean.

The research subjects who underwent abdominal surgery were divided into several parameters. There were no low MAP values, hypopnea, hypochloremia, hypocalcemia, and hypophosphatemia in the 11 patients. Hyperkalemia was observed in 1 patient, hyperchloremia in 2 patients, and hyperphosphatemia in 4 study patients. Only 1 patient failed to wean in the surgical group.

Hypokalemia and hypocalcemia were not found in all ICU/RICU patients with pulmonary infection indications. Hyponatremia was found in 3 patients, hypochloremia and hypomagnesemia in 2 patients, and hypophosphatemia in 1 patient. Hyperkalemia and hyperchloremia were obtained in 2 patients, hypercalcemia and hypermagnesemia in 1 patient, and hyperphosphatemia in 4 study patients. There was 1 patient who failed to wean in the pulmonary infection group.

The sexes of males and females did not show a significant difference in the two weaning groups, so there was no relationship between successful weaning and the sex of the research subjects. This relationship was analyzed using the Fisher's Exact test with an odds ratio (OR) of 2.67 (95% CI=0.22-0.33). There was no significant difference (unpaired t-test) between the mean ages of the successful weaning group and the failed weaning group, with a mean difference of 0.93 years (*P*=0.926).

The unpaired t-test showed no significant difference in the mean between the successful weaning group and the failed weaning group (*P*=0.997). BMI was combined into 2 groups, namely normal and abnormal. There was no significant correlation between BMI classification and invasive mechanical ventilation weaning (*P*=0.232) using the Fisher's Exact test. The OR value is also insignificant because it exceeds 1 (0.01-3.02) after the Haldane-Anscombe correction.[16]

Heart rate was significantly different between the successful and unsuccessful weaning groups with *P*=0.036 and a mean difference of ±37.5 mmHg. The failed weaning group had a higher pulse rate.

Table 2. Laboratory results and weaning from invasive mechanical ventilation

Characteristics	The mean/median at weaning		Average difference (95% CI)	*P*
	Succeed	Fail		
Hemoglobin	11.66±2.05	9.53±1.56	2.12 (-0.38 – 4.63)	0.093
Hematocrit	34.47±6.05	28.77±5.72	5.7 (-1.79 – 13.2)	0.13
Platelets (thousand)	233.5 (3-1.165)	408±236.32	---	0.181
Leukocytes	15.935 (7.470-48.830)	24.240±9.530.11	---	0.316
Urea	27 (13-244)	62.33±76.12	---	0.826
Creatinine	0.75 (0.4-8.6)	1.47±1.51	---	0.925
Sodium	135.96±4.27	136±8.19	0.04 (-5.74 – 5.81)	0.99
Potassium	3.85 (2.8-7.4)	5.06±1.27	---	0.077
Chloride	103.51±5.96	104.67±8.02	1.16 (-6.45 – 8.77)	0.758
Calcium	1.23±0.07	1.33±0.1	0.1 (0.01 – 0.19)	0.024
Magnesium	0.5 (0.5-2.6)	0.6 (0.6-2.7)	---	0.181
Phosphor	4.21±1.17	5.43±0.47	1.22 (-0.19 – 2.63)	0.087

Other vital sign parameters such as MAP, respiratory rate, and O_2 saturation had no significant association with weaning success (*P*>0.05). MAP had a normal average value in both groups, although there was a mean difference of ±22.89 mmHg between the two groups. The distribution of respiratory rate and O_2 saturation data in the two weaning groups was not normal, so it was impossible to calculate the mean difference. The MAP classification (low and normal) with a cut-off value of 65 mmHg did not have a significant relationship (*P*=0.187) with successful weaning.

The successful weaning group had similar proportions to the failed weaning group in sodium (*P*=0.281) and calcium (*P*=0.097). Even so, the OR value of calcium levels did not exceed one, namely 34.2 (1.08–1079.3). Potassium, chloride, and magnesium levels did not have a significant relationship with the success of invasive mechanical ventilation weaning (*P*>0.05). Phosphorus levels showed no significant relationship with successful weaning (*P*=0.38), and the OR value exceeded 0.38 (0.01–11.31). The calculation of the ORs for potassium and phosphorus was carried out after the Haldane-Anscombe correction (added 0.5 in all proportions) because there are zeros in table 2x2.[16]

Table 3. Classification of electrolytes and weaning from invasive mechanical ventilation

Characteristics	The mean/median at weaning		*P*	OR (95% CI)
	Succeed	Fail		
Classification of sodium				
Hyponatremia	9 (32.1%)	2 (66.7%)	0.281	0.24 (0.02 – 2.97)
Normal	19 (67.9%)	1 (33.3%)		
Classification of potassium				
Hypokalemia	9 (32.1%)	0 (0.0%)		
Normal	16 (57.1%)	2 (66.7%)	---	---
Hyperkalemia	3 (10.7%)	1 (33.3%)		
New classification				
Hypokalemia	9 (32.1%)	0 (0.0%)		
Normal	19 (67.9%)	3 (100.0%)	0.537	3.41 (0.16– 72.95)
Hyperkalemia	9 (32.1%)	0 (0.0%)		
Chloride classification				
Hypochloremia	4 (14.3%)	1 (33.3%)		
Normal	18 (64.3%)	1 (33.3%)	---	---
Hyperchloremia	6 (21.4%)	1 (33.3%)		
New classification				
Hypochloremia	4 (14.3%)	1 (33.3%)	0.422	0.33 (0.024–4.6)
Normal/Hyperchloremia	24 (85.7%)	2 (66.7%)		
Calcium Classification				
Normal	28 (100.0%)	2 (66.7%)	0.097	34.2 (1.08–1079.3)
Hypercalcemia	0 (0.0%)	1 (33.3%)		
Magnesium Classification				
Hypomagnesemia	21 (75)	2 (66.7%)		
Normal	7 (25%)	0 (0%)	---	---
Hypermagnesemia	0 (0.0%)	1 (33.3%)		
New classification				
Hypomagnesemia	21 (75.0%)	2 (66.7%)	1.000	1.5 (0.117–19.18)
Normal/hypermagnesemia	7 (25.0%)	1 (33.3%)		
Phosphorus classification				
Hypophosphatemia	---	0 (0.0%)		
Normal	---	0 (0.0%)	---	---
Hyperphosphatemia	---	3 (100.0%)		
New classification				
Hypophosphatemia	0 (0.0%)	0 (0.0%)	1.000	0.38 (0.01–11.31)
Normal/hyperphosphatemia	27 (96.4%)	3 (100.0%)		

Calcium is significantly associated with invasive mechanical ventilation weaning (*P*=0.024). Calcium values in the successful group were ±0.1 mmol/L lower compared to the failed weaning group. Other laboratory results parameters did not significantly correlate with weaning success (Table 2). Platelets had quite a large difference in values (mean and mean) in the two weaning groups, although not statistically significant (*P*=0.181). The electrolyte results were divided into several groups and analyzed using crosstabs (Table 3). Several parameters, such as potassium, chloride, magnesium, and phosphorus, were divided into two groups (normal and abnormal) because they did not meet the chi-square requirements for the 3x2 table. If there are still zeros (0) after redistribution, then the Haldane-Anscombe correction is used to calculate OR.[16]

Table 4. The relationship between magnesium and sodium, potassium and chloride

Laboratory	Magnesium Levels (meq/L)		*P*
	Low	Normal/High	
Sodium			
Hyponatremia	7 (30.4%)	4 (50.0%)	0.405
Normal	16 (69.6%)	4 (50.0%)	
Potassium			
Hypokalemia	8 (34.8%)	1 (12.5%)	0.379
Normal/hyperkalemia	15 (65.2%)	7 (87.5%)	
Chloride			
Hypochloremia	2 (8.7%)	3 (37.5%)	0.093
Normal/hyperchloremic	21 (91.3%)	5 (62.5%)	

The APACHE II scores calculated within 24 hours after the study subjects were admitted to the ICU/RICU were divided into 3 scores, namely physiological scores (A), age (B), and chronic disease scores (C). Score A has an abnormal distribution of data in both groups and has no significant relationship (*P*=0.975) with successful weaning, as does score B (*P*=0.875), score C (*P*=0.925), and the total score (*P*=0.826). The C score had a median value of zero and similar minimum and maximum limits in the two groups. The A and B scores tended to be higher in the group that successfully weaned, while the total score tended to be higher in the group that failed to wean, although not significantly different (*P*>0.05). The Fisher's Exact test, carried out on sodium, potassium, and chloride levels on magnesium levels, did not give significant results (Table 4) with value of *P* are 0.405, 0.379, and 0.093.

Table 5. The relationship between phosphorus and sodium, potassium and chloride

Laboratory	Phosphorus Levels (meq/L)			*P*
	Low	Normal	High	
Sodium				
Hyponatremia	1 (100.0%)	4 (21.1%)	6 (54.5%)	0.565
Normal	0 (0.0%)	15 (78.9%)	5 (45.5%)	
Potassium				
Hypokalemia	0 (0.0%)	7 (36.8%)	2 (18.2%)	0.979
Normal/hyperkalemia	1 (100.0%)	12 (63.2%)	9 (81.8%)	
Chloride				
Hypochloremia	0 (0.0%)	2 (10.5%)	3 (27.3%)	0.866
Normal/hyperchloremic	1 (100.0%)	17 (89.5%)	8 (72.7%)	

None of the study subjects experienced hypernatremia. The potassium and chloride groups were divided into 2 groups, namely, low and normal/high levels because they did not meet the chi-square requirements for the 3x2 table. Sodium, potassium, and chloride levels did not significantly correlate with the blood's phosphorus levels (Table 5).

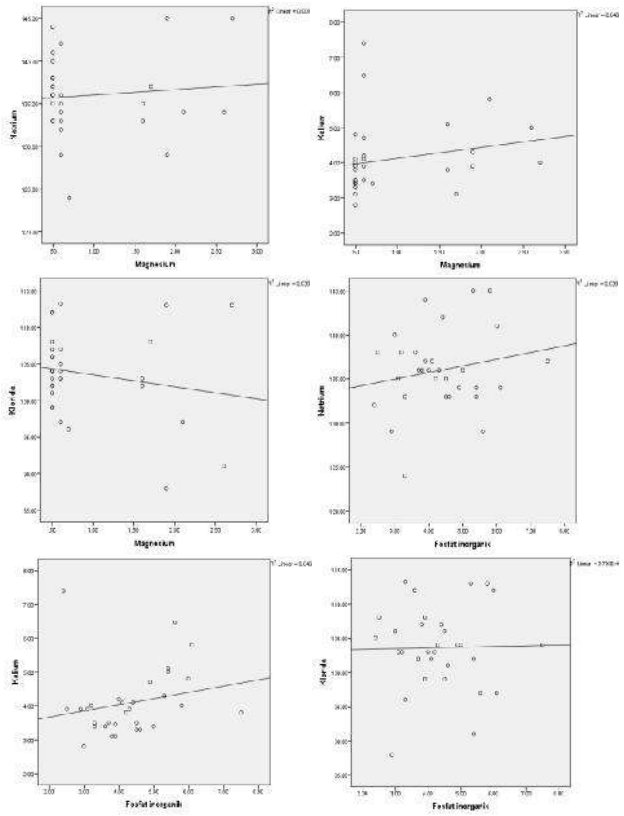

Figure 1. Scatter plot between magnesium and phosphate with other electrolytes

The value of *P* for the three electrolytes were 0.565, 0.979, and 0.866, respectively. The Kolmogorov-Smirnov test was used because it did not meet the chi-square requirements for a 2x3 table. The scatter plots between magnesium and phosphate with sodium, potassium, and chloride provide a picture consistent with the statistical test (Figure 1).

DISCUSSION

Due to limited funds and the feasibility of sampling, the total number of research subjects that could be analyzed was 31. Repeat laboratory examinations during weaning were not carried out because most patients were weaned before 24 hours of treatment in the ICU on RICU, especially post-surgery patients. Laboratory tests were also difficult to perform in non-surgical patients because the investigators were not always present during weaning. Characteristics of sex, age, BMI, BMI classification, MAP, MAP classification, respiratory frequency, O_2 saturation, blood laboratory results except for calcium levels, APACHE II A, B, C scores, and total were not significantly different between the two invasive mechanical ventilation weaning groups. The two groups had almost similar data.

Funk et al conducted a cohort study that included 257 patients with invasive mechanical ventilation during their stay in the ICU.[17] The main outcomes were divided into 3 weaning groups: simple, difficult, and prolonged weaning. Age and gender were not significantly different in the three weaning groups, with *P*=0.58. Another study by Vallverdu et al, conducted on 217 patients, showed that age characteristics were not significantly different in the two weaning groups (successful and failed), which were divided into 3 disease groups (acute respiratory failure, COPD, and neurologic disease).[18]

The gender characteristics of this study did not differ significantly between the 2 weaning outcome groups, similar to the study of Vallverdu et al, Funk et al, O'Brien et al, and Anzueto et al also had similar study subject characteristics.[17–20] These results indicated that age and type of gender were not confounding factor, although the number of subjects who failed to wean was only three.

BMI values and classifications did not differ significantly between the two invasive weaning groups. The average BMI value was only ±0.01 kg/m^2 with a *P* value of 0.997. The proportion of BMI classification after being divided into normal and abnormal did not differ significantly, with *P*=0.232 (95% CI=0.01–3.02). O'Brien et al conducted a prospective cohort study on 580 research subjects who were treated in the ICU using invasive mechanical ventilation and assessed the success of their first extubation based on their BMI group.[20]

With successful weaning, Anzueto et al found that BMI did not have a significant correlation with the duration of invasive mechanical ventilation, length of stay, or mortality.[19] However, a higher BMI increased complications during invasive mechanical ventilation, such as acute respiratory distress syndrome (ARDS) and kidney failure. In this case, BMI could be ruled out as a confounding factor.

The mean value of MAP in the successful weaning group was 99.89±21.51, higher than the failed weaning group (77±18.66), although not significantly different (*P*=0.088). Similarly, the MAP classification was not significantly different between the two weaning groups, and weaning success had no relationship with MAP score and classification. Khamiees et al studied 91 patients admitted to the ICU due to respiratory failure and obtained that pulse rate, respiratory rate, and MAP did not have a significant relationship with the successful weaning of these patients (Value of *P* are 0.81, 0.86, and 0.4, respectively).[21]

This study showed similar results except for pulse frequency. Both respiratory rate and MAP had *P*>0.05, while pulse frequency had *P*=0.036 when compared between the two weaning groups, with a mean difference of 37.55 (2.55–72.46). The mean pulse rate in the successful weaning group was within normal limits (95.9 beats/minute), while the failed weaning group tended to have tachycardia (133 beats/minute).

All laboratory parameters included in the study had no significant relationship (*P*>0.05) with weaning success except for blood calcium levels (*P*=0.024). The difference in mean blood calcium values in the two groups was 0.0 (0.01-0.19), with the successful weaning group having a lower value than the failed weaning group. Khamiees et al performed hemoglobin checks on all ICU patients who met the inclusion criteria and obtained a significant association with weaning success (*P*=0.01).[21]

However, the mean difference in hemoglobin was only ±1 mg/dL, so it was not clinically significant. In contrast to Table 2, hemoglobin levels did not have a significant relationship (*P*=0.093) with weaning success. Chang et al studied 175 subjects and compared the outcomes of successfully weaned patients and those who failed to wean (The outcome group had *P*=0.857 for white blood cells $10x10^3$/µl, 0.076 for BUN, mg/dL, and 0.706 for Creatinine, mg/dL).[22] Table 2 shows that the above parameters have no significant relationship with weaning success, in contrast to the results of Chang's study.[22]

Of the 31 study subjects found, 11 patients (35.5%) had hyponatremia, 9 patients had hypokalemia (29%), 5 patients (16.1%) had hypochloremia, no patients had hypocalcemia, 23 patients (74.2%) had hypomagnesemia, no patients had hypophosphatemia, 4 patients (12.9%) had hyperkalemia, 7 patients (22.6%) had hyperchloremia, 1 patient (0.03%) had hypercalcemia, 1 patient (0.03%) had hypermagnesemia, and 11 patients (35.5%) hyperphosphatemia. Fiaccadori et al observed a 20% incidence of hypomagnesemia in ICU patients.[10] Another study by Fiaccadori et al in 1994 pointed out that serum phosphorus levels in patients with COPD were lower than the control group (*P*<0.001).[11]

The APACHE II score did not have a significant correlation with weaning success in this study, including the A, B, and C scores which were the basic components. Study by Khamiees et al discovered that the APACHE II score was not significantly different in the two weaning groups with a *P* value of 0.46.[21] Likewise, a study by Chang et al in 175 subjects obtained a *P* value of 0.664 when comparing the APACHE II scores in the successful versus failed weaning group.[22] Keim-Malpass et al studied 1202 subjects and found that the difference in median APACHE II scores in patients living (14 [8-21]) and dying (19 [12-24]) during an ICU stay was significant, with a score difference of ±5.[23]

Gholyaf et al, Ryzen et al, and Sabatier et al stated that low magnesium levels did not affect sodium (*P*=0.405), potassium (*P*=0.379), and chloride (*P*=0.093) levels.[24–26] In contrast to the literature review by Huang et al in 2007, magnesium affected the potassium levels.[27] Hypomagnesemia is associated with hypokalemia by wasting potassium and increasing the effects of hypokalemia on target organs. No studies have assessed the relationship between phosphorus levels and levels of other electrolytes in the blood.

LIMITATION

Some of the limitations during the study were the number of research subjects, time to take blood samples for laboratory tests, and costs. The minimum number of subjects was 30, according to the rules for the number of pilot study samples. It was planned to collect more data, but the number of subjects was limited due to blood calcium, magnesium, and phosphorus examinations, which were not covered by state health insurance. The number of subjects who failed to undergo the weaning process was only a few (3 subjects) compared to the total study subjects (31 subjects), so confounding factors could not be removed. Many patients who can be taken as study subjects use postoperative invasive mechanical ventilation, so patients with respiratory failure or distress due to other diseases were less representative of the analysis results. This research was still descriptive, and confounding factors could not be analyzed.

CONCLUSION

The median value of magnesium levels in both invasive mechanical ventilation weaning groups (success and failure) was below the normal range.

The mean value of phosphorus levels in the successful weaning group was within normal limits, while in the failed weaning group was above normal values. Hypomagnesemia was found in both weaning groups, whereas hypophosphatemia was not found in both group. Pulse frequency and calcium levels had significantly lower values in the successful weaning group compared to the failed weaning group. The mean or median APACHE II A, B, C and total scores were not significantly different between the successful weaning groups and the failed weaning group.

Further research can be performed with a more balanced number of subjects between successful weaning and failed to wean, and also assisted by applying laboratory tests as service standards, especially magnesium and phosphorus. Subjects need to be more balanced so that the analysis can be more accurate. The application of magnesium and phosphorus examination as a service standard in the ICU/RICU can help pick up study subjects, especially outside working hours and holidays, and obtain data on subjects who are weaned other than working hours.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. Benditt JO. The neuromuscular respiratory system: physiology, pathophysiology, and a respiratory care approach to patients. Respir Care. 2006;51(8):829–37.
2. Barrett KE, Barman SM, Boitano S, Ganong WF, Brooks HL. Cellular and molecular basis for medical physiology. In: Kim E. Barrett, Barman SM, Boitano S, editors. Ganong's Review of Medical Physiology. 25th ed. New York: McGraw Hill Education; 2016. p. 1–156.
3. Barrett KE, Barman SM, Boitano S, Ganong WF, Brooks HL. Central and peripheral neurophysiology. In: Ganong's Review of Medical Physiology. 25th ed. New York: McGraw Hill Education; 2016. p. 1–156.
4. Haymaker W, Baer KA. Neurophysiologists. In: Haymaker W, Baer KA, editors. The founders of neurology: one hundred and thirty-three biographical sketches. Springfield IL: Charles C Thomas Publisher; 1953. p. 105–62.
5. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. Br J Anaesth. 1999;83(2):302–20.
6. Kawai M, Halvorson HR. Role of MgATP and MgADP in the cross-bridge kinetics in chemically skinned rabbit psoas fibers. Study of a fast exponential process (C). Biophys J. 1989;55(4):595–603.
7. Ko YH, Hong S, Pedersen PL. Chemical mechanism of ATP synthase. Magnesium plays a pivotal role in formation of the transition state where ATP is synthesized from ADP and inorganic phosphate. J Biol Chem. 1999;274(41):28853–6.
8. Moe SM. Disorders involving calcium, phosphorus, and magnesium. Prim Care. 2008;35(2):215.
9. Dhingra S, Solven F, Wilson A, McCarthy DS. Hypomagnesemia and respiratory muscle power. Am Rev Respir Dis. 1984;129(3):497–8.
10. Fiaccadori E, Del Canale S, Coffrini E, Melej R, Vitali P, Guariglia A, et al. Muscle and serum magnesium in pulmonary intensive care unit patients. Crit Care Med. 1988;16(8):751–60.
11. Fiaccadori E, Coffrini E, Fracchia C, Rampulla C, Montagna T, Borghetti A. Hypophosphatemia and phosphorus depletion in respiratory and peripheral muscles of patients with respiratory failure due to COPD. Chest. 1994;105(5):1392–8.
12. Aubier M, Murciano D, Lecocguic Y, Viires N, Jacquens Y, Squara P, et al. Effect of hypophosphatemia on diaphragmatic

contractility in patients with acute respiratory failure. N Engl J Med. 1985;313(7):420–4.
13. Gravelyn TR, Brophy N, Siegert C, Peters-Golden M. Hypophosphatemia-associated respiratory muscle weakness in a general inpatient population. Am J Med. 1988;84(5):870–6.
14. Zhao Y, Li Z, Shi Y, Cao G, Meng F, Zhu W, et al. Effect of hypophosphatemia on the withdrawal of mechanical ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. Biomed Rep. 2016;4(4):413–6.
15. Johanson GA, Brooks GP. Initial scale development: Sample size for pilot studies. Educ Psychol Meas. 2009;70(3):394–400.
16. Fagerland MW, Lydersen S, Laake P. Recommended confidence intervals for two independent binomial proportions. Stat Methods Med Res. 2015;24(2):224–54.
17. Funk GC, Anders S, Breyer MK, Burghuber OC, Edelmann G, Heindl W, et al. Incidence and outcome of weaning from mechanical ventilation according to new categories. Eur Respir J. 2010;35(1):88–94.
18. Vallverdú I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. Am J Respir Crit Care Med. 1998;158(6):1855–62.
19. Anzueto A, Frutos-Vivar F, Esteban A, Bensalami N, Marks D, Raymondos K, et al. Influence of body mass index on outcome of the mechanically ventilated patients. Thorax. 2011;66(1):66–73.
20. O'Brien JM, Philips GS, Ali NA, Aberegg SK, Marsh CB, Lemeshow S. The association between body mass index, processes of care, and outcomes from mechanical ventilation: a prospective cohort study. Crit Care Med. 2012;40(5):1456–63.
21. Khamiees M, Raju P, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. Chest. 2001;120(4):1262–70.
22. Chang YC, Huang KT, Chen YM, Wang CC, Wang YH, Tseng CC, et al. Ventilator dependence risk score for the prediction of prolonged mechanical ventilation in patients who survive sepsis/septic shock with respiratory failure. Sci Rep. 2018;8(1):5650.
23. Keim-Malpass J, Enfield KB, Calland JF, Lake DE, Clark MT. Dynamic data monitoring improves predictive analytics for failed extubation in the ICU. Physiol Meas. 2018;39(7):075005.
24. Gholyaf M, Basiri Z, Taghizadeh T, Nemati E, Taghipour M, Motalebi M. Magnesium level changes and its possible effects on the outcome of patients admitted to intensive care unit. Nephrourol Mon. 2017;9(4):e14007.
25. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. Crit Care Med. 1985;13(1):19–21.
26. Sabatier M, Pont F, Arnaud MJ, Turnlund JR. A compartmental model of magnesium metabolism in healthy men based on two stable isotope tracers. Am J Physiol Regul Integr Comp Physiol. 2003;285(3):R656-63.
27. Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol. 2007;18(10):2649–52.

Original Article

Correlation Between Body Composition and Peak Expiratory Flow Rate in First-Year Medical Students of Diponegoro University

Timothy Jordan[1], Darmawati Ayu Indraswari[2], Edwin Basyar[2], Buwono Puruhito[2]

[1]General Medicine Study Program, Faculty of Medicine, Universitas Diponegoro, Indonesia
[2]Department of Physiology, Faculty of Medicine, Universitas Diponegoro, Indonesia

Abstract

Background: Peak expiratory flow rate (PEFR) is one of the pulmonary ventilation parameters that affects quality of life. PEFR is known to be negatively affected by high body mass index (BMI) and waist circumference (WC). This study aimed to determine the correlation of BMI and WC with PEFR in first-year medical undergraduates at Diponegoro University.

Methods: This was a cross-sectional study held from October 5th to October 8th, 2020, which measured the BMI, WC, and PEFR of 169 first-year medical students at Diponegoro University. The BMI, WC, and PEFR were assessed using a digital scale, measuring tape, and Mini-Wright Peak Flow Meter (PFM), respectively. Spearman test was used for bivariate analysis, whereas the multiple regression method was used for multivariate analysis. The results are considered significant if *P*<0,05 for bivariate and F<0,05 for multivariate analysis. The IBM SPSS Statistics 26.0 Software was used for statistical analysis.

Results: Most of the subjects had normal BMI, with a mean value of 23.38 (±0.36) kg/m^2. As many as 71.6% of the subjects had normal WC. There was a correlation between BMI and PEFR (*P*=0.001) with a weak strength (R=0.260). As for BMI, WC also demonstrated a significant positive correlation (*P*<0.001) with a weak strength (R=0.342) towards PEFR. Simultaneously, both BMI and WC had a significant positive correlation (F<0.001) with a weak strength (R=0.361) towards PEFR.

Conclusion: Higher BMI and WC values coincided with higher PEFR values.

Keywords: body mass index, waist circumference, peak expiratory flow rate

Corresponding Author:
Darmawati Ayu Indraswari | Department of Physiology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia | darmawatiayu@gmail.com

Submitted: November 22nd, 2022
Accepted: March 9th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 177–82
https://doi.org/10.36497/jri.v43i3.517

INTRODUCTION

Peak expiratory flow rate is among the lung ventilation parameters that determine the quality of life.[1,2] PEFR is measured by previously asking the patient to inhale a deep breath, then exhale suddenly and powerfully into an instrument called mini-Wright PFM.[3,4] The result is expressed in L/minute and indicates the resistance of small respiratory airways.[2,3,5,6] Thus, a decrease in PEFR represents an airway obstruction, such as in those with asthma and chronic obstructive pulmonary disease (COPD).[5–7] PFM provides a more convenient and practical alternative for assessing airway obstruction compared to a spirometer, which is less available and requires a professional worker to operate it.[4,6,8] Besides obstruction, a decrease in PEFR also occurs in patients with reduced lung volume, such as those with pleural effusion and respiratory muscle weakness.[4]

Physiologically, PEFR is well-known to be affected by age, gender, and height.[3] Previous studies have demonstrated that PEFR can also be influenced by body weight, body surface area, BMI, WC, antioxidant and alcohol consumption, and smoking habits. BMI has an inverse relationship with PEFR, whether it is significant or not.[9–13] Overweight and obese individuals, who have higher BMI values than the normal population, have their thoracic cavity expansion restricted due to the excessive amount of fat. In android obesity, the upward displacement of the diaphragm also decreases lung volume. The decrease in maximum lung volume before expiration increases airway resistance and decreases PEFR.[14–16]

This relationship is seen in the flow-volume curve between PEFR and functional residual capacity, which describes that reduced lung volume correlates with reduced PEFR.[16,17] PEFR can also be negatively affected by WC, an indicator of central

obesity, by restricting diaphragm and lung expansion.[14,16] In addition, WC is a more reliable marker of PEFR reduction than BMI.[12] Both WC and BMI are convenient means of measuring body composition.[1,18] BMI represents adiposity with high specificity, but it cannot measure body fat distribution.[19,20] This pitfall is overcome by taking WC into account as a reliable indicator of visceral adiposity.[18,21]

The negative effects of obesity on PEFR are deteriorated the fact that the global prevalence of obesity in 2016 increased nearly three times compared with 1975, as shown by the surveillance conducted by the World Health Organization (WHO).[22] In Indonesia, *Riset Kesehatan Dasar* (Riskesdas) held in 2018 demonstrated that as many as 13.6% and 21.8% of its adult population were overweight and obese, respectively. Both values were higher than those in 2007 and 2013. Riskesdas 2018 also classified 31% of Indonesian adults >15 years old as having central obesity, and the value was also higher than that in 2007 and 2013.[23]

Considering the increased prevalence of obesity and its related pulmonary complications, this study aimed at determining the relationship between body composition parameters, which are BMI and WC, towards PEFR.

METHODS

This cross-sectional study was held from October 5th to October 8th, 2020, in the Faculty of Medicine, Diponegoro University, Semarang. This study measured the BMI, WC, and PEFR of 169 first-year medical students at Diponegoro University. Subjects were taken using the consecutive sampling method and had previously been asked to consent using *Google Forms* as an online platform. Male and female first-year medical students aged more than 16 who agreed to join the study were included. Subjects with prior or current COPD, current upper or lower respiratory tract infections, or those with a history of smoking were excluded.

The *Omron* digital scale, measuring tape, and Mini-Wright PFM were used to determine BMI, WC, and PEFR, respectively. BMI was classified using WHO criteria for the Asian population into four categories: underweight (BMI <18.5 kg/m^2), normal (BMI 18.5 to 22.9 kg/m^2), overweight (BMI 23.0 to 27.5 kg/m^2), and obese (BMI >27.5 kg/m^2).[24] WC was classified using International Diabetes Foundation criteria for the Asian population into normal (≤90 cm for men, ≤80 cm for women), and central obesity (>90 cm for men, >80 cm for women).[25] PEFR was estimated by first requesting that the subject breathed in a full breath before blowing it strongly into the PFM. The best value was taken from three consecutive measurements.[3,4] Ethical clearance was acquired from the Medical and Health Research Ethics Commission, Faculty of Medicine, Diponegoro University No. 49/EC/KEPK/FK-UNDIP/IV/2020.

IBM SPSS Statistics 26.0 Software was used for statistical analysis and the Kolmogorov-Smirnov test was used to assess the data distribution's normality. The Pearson test was used when the data was distributed normally, whereas the Spearman test was used when the data was not normally distributed. For multivariate analysis, the multiple regression method was used. The results were considered significant if *P*<0,05 for bivariate analysis and F<0,05 for multivariate analysis.

RESULTS

We collected 169 first-year medical students from Diponegoro University as subjects for this study. The mean BMI was 23.38 kg/m^2, and the values ranged from 16.00 to 38.90 kg/m^2. As many as 71.6% of the subjects in this study show normal WC. The mean PEFR was 444.97 L/minute (Table 1).

Table 1. Characteristics of age, BMI, WC and PEFR of the subjects

Characteristic	Mean±SD	Median (Min–Max)
Age (years)	18.80±0.63	19.00 (17–21)
BMI (kg/m^2)	23.38±0.36	22.70 (16.00–38.90)
WC (cm)	79.93±0.89	78.00 (62.0–120.0)
PEFR (L/minute)	444.97±8.80	410.00 (155–740)

Note: Min = Minimum; Max = Maximum; SD = Standard deviation

There were 64 men and 105 women. The age range was from 17 to 21 years old, with the largest proportion (45.0%) coming from 19-year-olds (Table 2).

Table 2. Characteristics of gender, age, BMI, and WC of the subjects

Characteristic	N (%)
Gender	
Men	64 (37.9%)
Women	105 (62.1%)
Age (years)	
17	5 (3.0%)
18	58 (34.3%)
19	76 (45.0%)
20	26 (15.4%)
21	4 (12.4%)
BMI (kg/m^2)	
Underweight	20 (11.8%)
Normal	69 (40.8%)
Overweight	46 (27.2%)
Obese	34 (20.1%)
WC (cm)	
Normal	121 (71.6%)
Central obesity	48 (28.4%)
Total	169 (100.0%)

Note: N = Sum

Kolmogorov-Smirnov normality test for BMI, WC, and PEFR did not show normal data distributions. Thus, all of them were directed to Spearman's test to determine their intervariable relationships. BMI had a significant positive Spearman's correlation (*P*=0.001) with weak strength (R=0.260) towards PEFR. As for BMI, WC also showed a significant positive correlation (*P*<0.001) with weak strength (R=0.342) towards PEFR (Table 3).

Table 3. Bivariate analysis between BMI, WC, and PEFR

Variable	*P*	Correlation coefficient (R)
BMI PEFR	0.001[a]	0.260
WC PEFR	<0.001[a]	0.342

Note: [a]Significant correlation with Spearman test if *P* <0.05

Simultaneously, both BMI and WC had a significant positive correlation (F<0.001) with weak strength (R=0.361) towards PEFR (Table 4).

Table 4. Multivariate analysis between BMI, WC, and PEFR

F (multiple regression)	R	Correlation strength
<0.001[a]	0.361	Weak

Note: [a]Significant correlation if F<0.05

DISCUSSION

This study demonstrated a positive correlation between each BMI and WC towards PEFR with both *P*<0.001. These outcomes contradicted past studies, which showed that a rise in BMI values was related to reduced PEFR levels.[9–13,26] There was a study that showed no significant correlation between them.[27] We found two studies conducted by Dharamshi and Archana that demonstrated a positive correlation between BMI and PEFR, as of this study. However, Dharamshi explained that the lack of overweight and obese samples contributed to the difference in his result with previous researches.[28]

That case is the same as this study, where most of the subjects had normal BMI and WC. Only 12% and 28% of the subjects were underweight and had central obesity, respectively. Although the study by Archana showed a positive correlation in general, more specific analyses of each of the BMI categories showed that BMI negatively correlated with PEFR when the BMI exceeded +2 SD. This implied that an increase in BMI starts to reduce PEFR in overweight people.[29]

As for BMI, this study also showed that WC had a positive and significant correlation with PEFR which differed from previous studies. Rai showed a negative correlation between WC and PEFR in male subjects.[14,30] A meta-analysis comprising 10 studies that assessed the correlation between WC and lung function exhibited a negative correlation between WC and forced expiratory volume in 1 second (FEV_1). Since FEV_1 is the expiration rate on the first second, it represents the maximum expiratory flow and thus is strongly associated with PEFR.[17,31,32] Those studies are consistent with the idea that increased WC restricts lung expansion.[14,16,19–21,33]

Others showed no significant correlation, implying that WC is an independent factor of PEFR.[34,35] The significant positive correlation between BMI and WC towards PEFR in our study may be explained by the greater number of subjects with normal BMI and WC in comparison to those with overweight and obesity.

LIMITATION

A lot of contradictions with the previous studies may also stem from the fact that this study was held

during the Coronavirus Disease 2019 global pandemic, where activities inside the faculty were heavily restricted. Therefore, several measurements such as WC and body height for calculating BMI were done by the subjects themselves without direct supervision. Although the procedure had been provided online, errors were still possible and may affect the final result of this study. PEFR was measured on the spot, and the subjects had been told how to use the PFM. However, it was still possible that they did not inhale a deep breath before exhaling or did not exhale powerfully. Besides the aforementioned technical and procedural problems, an even sample distribution for each of the BMI or WC categories is required to enhance the validity of the data. This can be achieved by increasing the sample size. Other variables such as body weight, body surface area, and alcohol consumption should also be taken into account to enhance the validity of the results.

CONCLUSION

Higher BMI and WC values coincide with higher PEFR values. Studies involving more variables, including those related to pulmonary ventilation such as FEV_1, are required to confirm the validity of this study.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

None.

REFERENCES

1. Ackland TR, Lohman TG, Sundgot-Borgen J, Maughan RJ, Meyer NL, Stewart AD, et al. Current status of body composition assessment in sport: review and position statement on behalf of the ad hoc research working group on body composition health and performance, under the auspices of the I.O.C. Medical Commission. Sports Med. 2012;42(3):227–49.
2. Hall JE. Guyton and Hall Textbook of Medical Physiology. 13th ed. Philadelphia: Elsevier Health Sciences; 2015.
3. Adeniyi BO, Erhabor GE. The peak flow meter and its use in clinical practice. African Journal of Respiratory Medicine. 2011;6(1).
4. Myatt R. Measuring peak expiratory flow rate: what the nurse needs to know. Nurs Stand. 2017;31(20):40–4.
5. Mehta B, Garg K, Ambwani S, Bhandari B, Bhagat OL. Peak expiratory flow rate: A useful tool for early detection of airway obstruction in school children. Open Med J. 2016;3(1):159–65.
6. Tian J, Zhou Y, Cui J, Wang D, Wang X, Hu G, et al. Peak expiratory flow as a screening tool to detect airflow obstruction in a primary health care setting. Int J Tuberc Lung Dis. 2012;16(5):674–80.
7. Dancer R, Thickett D. Pulmonary function tests. Medicine. 2012;40(4):186–9.
8. Scottish Intercollegiate Guidelines Network, British Thoracic Society. British guideline on the management of asthma : a national clinical guideline. Sign 158; 2019. p. 208.
9. Jones RL, Nzekwu MMU. The effects of body mass index on lung volumes. Chest. 2006;130(3):827–33.
10. Joshi V, Shah S. Effect of body mass index (BMI) on peak expiratory flow rate in young adults. IAIM. 2016;3(5):85–8.
11. Mungreiphy NK, Dhall M, Tyagi R, Saluja K, Kumar A, Tungdim MG, et al. Ethnicity, obesity and health pattern among Indian population. J Nat Sci Biol Med. 2012;3(1):52–9.
12. Saxena Y, Sidhwani G, Upmanyu R. Abdominal obesity and pulmonary functions in young Indian adults: a prospective study. Indian J Physiol Pharmacol. 2009;53(4):318–26.
13. Shenoy JP, Shivakumar J, Kalpana B, Bhat SK. Impact of adiposity markers on peak expiratory flow rate in young adult South Indian females.

Muller Journal of Medical Sciences and Research. 2014;5(2):121–4.
14. Koenig SM. Pulmonary complications of obesity. Am J Med Sci. 2001;321(4):249–79.
15. Rabec C, de Lucas Ramos P, Veale D. Respiratory complications of obesity. Arch Bronconeumol. 2011;47(5):252–61.
16. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol (1985). 2010;108(1):206–11.
17. Wehrmeister FC, Menezes AMB, Muniz LC, Martínez-Mesa J, Domingues MR, Horta BL. Waist circumference and pulmonary function: a systematic review and meta-analysis. Syst Rev. 2012;1(1):55.
18. Wells JCK, Fewtrell MS. Measuring body composition. Arch Dis Child. 2006;91(7):612–7.
19. Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin PJ, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. Int J Obes (Lond). 2010;34(5):791–9.
20. Pasco JA, Nicholson GC, Brennan SL, Kotowicz MA. Prevalence of obesity and the relationship between the body mass index and body fat: cross-sectional, population-based data. PLoS One. 2012;7(1):e29580.
21. Berker D, Koparal S, Işik S, Paşaoğlu L, Aydin Y, Erol K, et al. Compatibility of different methods for the measurement of visceral fat in different body mass index strata. Diagn Interv Radiol. 2010;16(2):99–105.
22. Levesque RJR. Obesity and Overweight. In: Levesque RJR, editor. Encyclopedia of Adolescence. New York, NY: Springer New York; 2011. p. 1913–5.
23. Kementerian Kesehatan RI. Hasil utama Riskesdas 2018. Jakarta: Kementerian Kesehatan RI; 2018.
24. Satyanarayana B, Reddy VD, Syamala E. Peak expiratory flow rate; the effect of smoking on younger & middle aged males. Int J Res Med Sci. 2013;1(4):441–2.
25. World Health Organization. Waist circumference and waist-hip ratio : report of a WHO expert consultation]. World Health Organization. Geneva: World Health Organization; 2011. p. 8–11. Available from: https://apps.who.int/iris/handle/10665/44583
26. Kaur H, Singh J, Makkar M, Singh K, Garg R. Variations in the peak expiratory flow rate with various factors in a population of healthy women of the Malwa Region of Punjab, India. J Clin Diagn Res. 2013;7(6):1000–3.
27. Wahyu I, Mourisa C. Hubungan nilai arus puncak ekspirasi dengan indeks massa tubuh pada mahasiswi Fakultas Kedokteran Universitas Muhammadiyah Sumatera Utara. Jurnal Ibnu Sina Biomedika. 2017;1(1):57–68.
28. Dharamshi HA, Faraz A, Ashraf E, Abbas Mohsin Ali A, Ali Merchant Rameez M, Muhammad Ali Abidi S, et al. Variation of peak expiratory flow rate with body mass index in medical students of Karachi, Pakistan. Int Arch Med. 2015;8(121):1–5.
29. Nepal A. Correlation of peak expiratory flow rate with body mass index in school children of a government school of Kathmandu. Journal of Kathmandu Medical College. 2019;8(1):37–40.
30. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. Clin Res Cardiol. 2006;95(3):136–47.
31. Llewellin P, Sawyer G, Lewis S, Cheng S, Weatherall M, Fitzharris P, et al. The relationship between FEV1 and PEF in the assessment of the severity of airways obstruction. Respirology. 2002;7(4):333–7.
32. Shin SY, Ho YJ, Kim SJ, Yoo KH. The relationship between FEV1 and PEFR in the classification of the severity in COPD patients. Tuberc Respir Dis (Seoul). 2005;58(5):507–14.
33. Lavie CJ, De Schutter A, Patel DA, Romero-Corral A, Artham SM, Milani R V. Body composition and survival in stable coronary heart disease: impact of lean mass index and body fat in the “obesity paradox.” J Am Coll Cardiol. 2012;60(15):1374–80.

34. Aryana IGPS, Nugraha KAW, Putra AAGORK, Kusumawardani IAJD, Kuswardhani RAT, Astika N, et al. The association between Central Obesity & PEFR. International Journal of Medical and Health Science. 2018;4:1–20.
35. Saxena Y, Purwar B, Upmanyu R. Adiposity: determinant of peak expiratory flow rate in young Indian adults male. Indian J Chest Dis Allied Sci. 2011;53(1):29–33.

Original Article

Is Vaccination Related to The Cure Rate of COVID-19 Patients with Comorbidities?

Mia Herdiyani Achmad, Reviono, Yusup Subagio Sutanto, Jatu Aphridasari, Windu Prasetyo

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, Dr. Moewardi General Hospital Surakarta, Indonesia

Abstract

Background: Prior vaccination can prevent a COVID-19 patient from falling into moderate, severe, and critical conditions. The effect of vaccination on COVID-19 patients' recovery has been widely studied. However, its correlation in critically severe COVID-19 patients with comorbidity has not been fully understood yet. This study aims to determine the correlation of vaccination in critically severe COVID-19 patients with comorbidity of hypertension and/or Diabetes Mellitus (DM).

Methods: A retrospective cohort study was conducted in critically severe COVID-19 patients with hypertension and/or DM treated in Dr. Moewardi Hospital, Surakarta, Indonesia from March 2021 to September 2021. The data were taken from patients' medical records. We analyzed all data statistically with Chi-Square and Fisher's exact test, and $P<0.05$ was considered significant.

Results: There were 489 patients included in our study, 247 patients with hypertension and DM, and 242 patients without comorbidities. Vaccination status was significantly associated with the cure rate of critically severe COVID-19 patients with hypertension ($P=0.018$), but not with DM ($P=0.606$). There was no significant association between age to the cure rate of critically severe COVID-19 patients with hypertension and DM ($P=0.953$). Vaccination status was related among patients with comorbidities and without comorbidities ($P<0.001$).

Conclusion: Vaccination was significantly correlated with the cure rate of moderate to critically severe COVID-19 patients with hypertension and without comorbidities.

Keywords: COVID-19, cure rate, diabetes, hypertension, vaccination

Corresponding Author:
Mia Herdiyani Achmad | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret / Dr. Moewardi General Hospital, Surakarta, Indonesia | miaherdiyaniachmad@gmail.com

Submitted: May 27th, 2022
Accepted: March 15th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 183–9
https://doi.org/10.36497/jri.v43i3.324

INTRODUCTION

The World Health Organization (WHO) has declared COVID-19 as a pandemic since March 11, 2020.[1] Its clinical manifestations are diverse ranging from asymptomatic to fatal complications, such as acute respiratory distress syndrome (ARDS) and respiratory failure.[1,2]

The common comorbidities are hypertension (15.6%), diabetes mellitus (7.7%), and cardiovascular disease (4.7%). Approximately 44.5% of diabetes patients and 41,7% of hypertension patients are included in critical cases. Research in Indonesia stated that hypertension, diabetes mellitus (DM), and cardiovascular disease are the most common comorbidities, which are then related to the severity of symptoms. However, its role in mortality and treatment duration has not been widely known yet.[3–5] Various attempts have been made to develop SARS-CoV-2 vaccines in recent decades.[3]

The SARS-CoV-2 antigen vaccine can prevent COVID-19 infection and/or minimize its morbidity.[6] This study aimed to determine the relationship between COVID-19 vaccination and the recovery of moderate, severe, and critical COVID-19 patients with comorbid factors.

METHODS

The study was a retrospective cohort, taking medical records of moderate, severe, and critical COVID-19 patients undergoing intensive care in the isolation room from 1st March to 30th September 2021 at Dr. Moewardi Hospital, Surakarta. The sample size was measured using total purposive sampling.

The inclusion criteria were adult patients more than 18 years old, patients with hypertension and/or DM, patients without comorbidities, patients with a history of vaccination, patients undergoing treatment in isolation rooms with confirmed moderate, severe, and critical COVID-19 cases, and a patient who

underwent laboratory examination (GDP, G2PP, HbA1C, D dimer). The exclusion criteria were patients with absent or incomplete medical records and non-confirmed COVID-19. It was approved by the Ethics Feasibility Committee of the Dr. Moewardi Hospital, Faculty of Medicine, Sebelas Maret University, Surakarta in January 2022 with the ethical approval number 26/I/HREC/2022.

The data was statistically analyzed using SPSS version 25.0. Kolmogorov-Smirnov Test was used to determine the normality. The hypothesis test was Chi-square/Fischer's exact test. The confidence interval was 95%. The value of *P*<0.05 was declared as a statistically significant relationship.

RESULTS

This study analyzed 489 moderate, severe, and critical COVID-19 patients undergoing treatment in Melati 1 isolation room at Dr. Moewardi Hospital Surakarta from 1st March to 30th September 2021. Among them, 247 patients have hypertension and/or DM and 242 patients have no comorbidities.

The median value of patients' age was 47 (18–87) years old. The patients were mostly female accounting for 320 patients (65.4%). In this study, most participants (50.7%) had not been vaccinated against COVID-19 with the most comorbidities being DM (20.2%) and the living outcomes were 55.5% (Table 1).

Table 1. Characteristics of Subjects (N=489)

Characteristics	Result
Age (years) [median (min-max)]	47 (18–87)
Gender	
Male	169 (34.6%)
Female	320 (65.4%)
Vaccine Status	
No Vaccine	248 (50.7%)
1st Vaccine	34 (7.0%)
2nd Vaccine	207 (42.3%)
Comorbid	
Hypertension	89 (18.2%)
Diabetes	99 (20.2%)
Hypertension and Diabetes	59 (12.1%)
Without comorbidities	242 (49.5%)
Outcome	
Non-survivor	220 (45.0%)
Survivor	269 (55.0%)

Based on age, patients who were non-survivor tended to be older than those who survived. The median age of patients with both comorbidities was 61 (19–87) years old in non-survivor and 58 (19–79) years old in surviving patients. There was no significant difference (*P*=0.953) in the age of non-survivor and survivor patients. In patients with both comorbidities and no history of vaccines, 85.6% were non-survivor and 14.4% were survivors.

Table 2. The correlation between the vaccination status of moderate, severe, and critical COVID-19 patients and the outcome (N=489)

Vaccination status	N	Non-survivor	Survivor	*P*
1st Vaccine with HT and DM	21	18 (85.7%)	3 (14.3%)	<0.001*
1st Vaccine without comorbidities	13	3 (23.1%)	10 (76.9%)	
2nd Vaccine with HT and DM	31	21 (67.7%)	10 (32.3%)	
2nd Vaccine without comorbidities	176	3 (1.7%)	173 (98.3%)	
No Vaccine with HT and DM	195	167 (85.6%)	28 (14.4%)	
No Vaccine without comorbidities	53	8 (15.1%)	45 (84.9%)	

Note: **Chi-square* - significant if *P*<0.05; HT=hypertension; DM=diabetes mellitus

While in patients with 1st vaccine and 2nd dose vaccines, non-Survivor occurred in 85.7% and 67.7% were patients, respectively. There was a significant relationship (*P*=0.043) between vaccination status in moderate, severe, and critical COVID-19 patients with comorbid on their recovery. Around 88.9% of patients with comorbid hypertension complicated with DM who have not been vaccinated were dying. Non-Survivor occurred in patients with the 1st dose and 2nd dose was 80.0% and 55.6%, respectively. It means that the vaccination status of COVID-19 patients with moderate or higher severity levels combined with both comorbidities was not significantly correlated to its recovery. It was known that COVID-19 survivors were mostly patients with 2nd vaccine without comorbidities counted as 98.3%. It also had a higher cure rate up to 32.3%. There was a significant relationship (*P*≤0.001) between the vaccination status of moderate, severe, and critical COVID-19 patients with comorbid factors and no comorbidity to its outcome (Table 2).

It was also known that COVID-19 survivors were mostly patients without comorbidities (94.2%),

while non-survivor subjects were mostly patients with comorbid hypertension and DM (83.4%). There was a significant relationship (*P*≤0.001) between comorbid factors with the recovery outcome (Table 3).

Table 3. The correlation between comorbidities of moderate, severe, and critical COVID-19 patients and the outcome

Comorbidities	N	Non-survivor	Survivor	*P*
With comorbidities HTand/or DM	247	206 (83.4%)	41 (16.6%)	<0.001*
Without comorbidities	242	14 (5.8%)	228 (94.2%)	

Note: *Chi-square/Fisher exact test - significant at *P*<0.05; HT= hypertension; DM= diabetes mellitus

The survival rate of patients with both comorbidities who had not been vaccinated was only 14.4%. The survival rate of patients who were vaccinated with the 1st dose and 2nd dose was 14.3% and 32.3%, respectively. Vaccination status was significantly related to the recovery of moderate, severe, and critical COVID-19 patients with comorbid hypertension and/or DM (*P*=0.043). On the other hand, the survival rate of patients with hypertension who have not been vaccinated was 13.2%. In patients with the 1st dose and 2nd dose vaccine, the survival rate was 0% and 41.7%, respectively. The vaccination status was significantly related to the recovery status of moderate, severe, and critical COVID-19 patients with hypertension (*P*=0.018) (Table 4).

Table 4. The correlation between vaccination status of moderate, severe, and critical COVID-19 patients with comorbidities and the outcome

Characteristics	Non-survivor	Survivor	*P*
Vaccination (All Comorbidities)			
No Vaccine	167 (85.6%)	28 (14.4%)	
1st Vaccine	18 (85.7%)	3 (14.3%)	0.043*
2nd Vaccine	21 (67.7%)	10 (32.3%)	
Age (Hypertension)			
No Vaccine	59 (86.8%)	9 (13.2%)	
1st Vaccine	9 (100.0%)	0 (0.0%)	0.018*
2nd Vaccine	7 (58.3%)	5 (41.7%)	
Age (DM)			
No Vaccine	68 (82.9%)	14 (17.1%)	
1st Vaccine	5 (71.4%)	2 (28.6%)	0.606
2nd Vaccine	9 (90.0%)	1 (10.0%)	
Age (DM+Hypertension)			
No Vaccine	40 (88.9%)	5 (11.1%)	
1st Vaccine	4 (80.0%)	1 (20.0%)	0.051
2nd Vaccine	5 (55.6%)	4 (44.4%)	

Note: *Chi-square - significant at *P*<0.05

Table 5 showed that non-survivor subjects tended to be older, with the median age of subjects with comorbid hypertension and DM being 61 (19–87) years, while the median age of subjects living was 58 (19–79) years (*P*=0.953). The average age of COVID-19 subjects with comorbid hypertension whom non-survivor was 60.28±13.13 years, while the survivor was 60.93±10.25 years (*P*=0.862). Based on their vaccination status, there was no significant difference in patients who had not been vaccinated (*P*=0.640), received 1st dose, and 2nd dose (*P*=0.687).

Table 5. The correlation between age and vaccination status of moderate, severe, and critical COVID-19 patients with comorbidities and the outcome

Characteristics	Non-survivor (year)	Survivor (year)	*P*
Age (All Comorbidities)[a]	61 (19–87)	58 (19–79)	0.327
Age (Hypertension)[a]	60.28±13.13	60.93±10.25	0.862
No Vaccine[a]	59.59±13.18	57.44±9.28	0.640
1st Vaccine[b]	61.89±12.08	-	-
2nd Vaccine[a]	64.00±15.11	67.20±9.63	0.687
Age (DM)[a]	60.68±9.72	55.82±12.96	0.080
No Vaccine[a]	60.09±10.01	55.07±13.15	0.110
1st Vaccine[b]	63 (52–63)	52 (46–68)	0.228
2nd Vaccine[b]	65 (54–78)	74 (74–74)	0.384
Age (DM+Hypertension)[a]	61.47±8.77	67.40±7.97	0.982
No Vaccine[a]	61.40±9.09	58.40±8.96	0.490
1st Vaccine[b]	62 (56–72)	67 (67–67)	0.480
2nd Vaccine[a]	60.80±8.93	63.75±7.14	0.609

Note: [a]Uji Mann-Whitney; [b]Uji independent t-test

The average age of non-survivor subjects with DM comorbidities was 60.68±9.72 which was older than those who survive (*P*=0.080). Based on their vaccination status, there was no significant difference in patients who had not been vaccinated (*P*=0.110), received 1st dose (*P*=0.228), and 2nd dose (*P*=0.384). The average age of COVID-19 patients with comorbid hypertension complicated with DM who were non-survivor was 61.47±8.77 years, while for those who were survivors was 67.40±7.97 years (*P*=0.982). Based on their vaccination status, there was no significant difference in patients who had not been vaccinated (*P*=0.490), received 1st dose (*P*=0.480), and 2nd dose (*P*=0.609). There was no significant relationship between age and vaccination status in moderate, severe, and critical COVID-19 patients with or without comorbidities on its recovery.

DISCUSSION

Caifang et al, and Gili et al, showed that S can prevent the severity of COVID-19.[7,8] Sowmya et al, stated patients without comorbidities and who had been vaccinated showed better recovery.[9] Christian et al, concluded that vaccination in hypertension patients required more research to determine its effectiveness. This study found that there was a significant relationship between vaccination and recovery in moderate to critical COVID-19 patients with comorbid factors (hypertension and diabetes mellitus) and without comorbidities (*P*≤0.001). It was known that COVID-19 survivor were mostly patients with 2nd vaccine without comorbidities counted 98.3%, while non-survivor was mostly those with comorbidities who had not been vaccinated yet (85.6%) or only received the 1st vaccine (85.7%).

Hypertension is strongly correlated with lower antibodies. There is a similar mechanism of immune dysfunction in hypertension and vaccination's inappropriate response. Hypertension was previously found to be correlated with worse outcomes, suggesting higher morbidity as well as mortality in COVID-19 infection, and thus may be involved in the development of an immunologic response to vaccination.[10,11]

The prevalence of DM in COVID-19 patients ranges from 8.2% to 10.3%. In several studies, the presence of DM in COVID-19 was stated as an independent factor associated with severity and increased mortality. A meta-analysis of 33 studies concluded that DM in COVID-19 was associated with a twofold increased risk of non-survivor and disease severity, compared to patients without DM.[12]

The success of vaccination can be seen in COVID-19 patients without comorbidities as its cure rate was better than patients with comorbidities. It was also shown that 94.2% of patients without comorbidities stayed survivors, while 83.4% of patients with comorbid hypertension and DM were non-survivor (*P*≤0.001). In 2021, Irawaty et al showed that patients with comorbid hypertension and DM had a lower cure rate than those without comorbidities which were aligned with our study.

SARS-CoV-2 vaccination mostly targets glycoprotein or protein S as the main inducer of antibodies. The S protein-based vaccines induce antibodies that block both the viral receptor binding and the uncoating viral genome. The C-terminal domain of the S1 subunit of the coronavirus delta represents a dominant immune region. This region exhibits the strongest neutralization.[11–13]

Protein S has been known to have a big role in promoting protective immunity during SARS-CoV2 infection by inducting antibodies and T-cells. Glycoprotein S is believed to be the most promising candidate for CoV vaccine composition. Other structural proteins affect the immunogenicity of protein S or ACE2 receptor-binding which is an important initial step for viruses to access host cells. Both RBD-containing recombinant protein and RBD-encoding recombinant vector have superior abilities to induce neutralizing antibodies which can be used to develop an effective SARS-CoV vaccine.[11–13]

This research found vaccination status was significantly related to the recovery of moderate, severe, and critical COVID-19 patients with comorbid hypertension and/or DM (*P*=0.043) and with hypertension only (*P*=0.018). Patients with 2nd dose of the vaccine had a higher cure rate than patients with 1st dose and who had not been vaccinated yet. The vaccination triggers a memory immune response that eliminates the SARS-CoV- 2 virus and improves its clinical outcomes in hypertensive patients. The ACE2 converts angiotensin II to angiotensin I-VII to neutralize the inflammatory effects of angiotensin II, reduce the level of pro-inflammatory cytokine interleukin 6, increase the anti-inflammatory and antioxidant role of angiotensin I-VII, increase the concentration of alveolar surfactant protein D, and induce vasodilation.[14,15]

On the other hand, the vaccination was not significantly correlated in DM patients (*P*=0.606) or patients with complications of hypertension with DM (*P*=0.051). The results of this study are not in line with previous studies that showed an impaired antibody response to influenza and hepatitis B vaccines in DM patients. Recent studies showed people with DM can enhance an appropriate immune

response post-vaccination. Several case-control studies showed that the effectiveness and safety of the pneumococcal vaccine ranged from 56% to 81%. The effectiveness of the 23-valent Pneumococcal Polysaccharide Vaccine (PPV23) was 84% in people with DM. The PPV23 effectively prevents pneumococcal disease and reduces the utilization of medical services in patients aged 75 years old or older with DM. Young and elderly adults with DM have been shown to promote optimal B cell responses to the seasonal influenza vaccine.[16–19]

Based on the existing theory, DM causes glucotoxicity and endothelial damage due to inflammation, and oxidative stress. Thereby, thromboembolic complication increases putting organ vitals at a high risk of malfunction. Microangiopathy in DM may also reduce lung compliance which in turn will interfere with air exchange in the lungs. There are also some changes in the respiratory in DM patients that affect lung volume and lung diffusion capacity. DM and hypertension are chronic inflammations that further exacerbate the dysfunction of T cells, dendritic cells and other inflammatory factors.[19,20]

Blood sugar control also affects the mortality of COVID-19 patients with DM, as in a study of 10,926 on COVID-19 which concluded that there was an increased risk of non-survivor in patients with poor HbA1c. A multicenter retrospective research in China also found that one of the independent factors of mortality in COVID-19 patients was the high fasting glucose levels at admission (≥7.0 mmol/L OR 126 mg/dL). DM was associated with the risk of COVID-19 with severe symptoms including the risk of ARDS, use of the ICU room, and the need for a ventilator.[16,18]

All age groups are at risk of being infected with COVID-19. Based on the research, it was known that non-survivor patients tended to be older than those who survived, even though the data was not significantly correlated (P=0.953). An epidemiological analysis showed that 77.8% of COVID-19 patients were in the age range of 30 to 69 years with the highest proportion in the age of 50 to 60 years.

The infection rate in children was considered relatively low. High severity happens in patients aged >60 years old, living in nursing homes or long-term care facilities, and had chronic diseases. Male patients dominated (56.9%) cases. The highest mortality rate happens in patients aged >70 years old, regardless of the presence of a chronic medical condition, such as 32% of cardiovascular disease, 30% of DM, and 18% of chronic lung disease. Other conditions that put people at high risk were cancer, obesity, kidney disease, sickle cell disease, and other immunocompromised conditions.[2,21–23]

LIMITATION

There were some limitations of the study. First, it was a retrospective cohort research in which observations were made indirectly by relying on medically recorded data only. Thus, we could not control the data quality. In addition, indirect observations made it difficult to accurately determine the effective time of the vaccine. Second, this study did not rule out the type and the onset of the vaccine. The effect of antibodies after their administration might affect the outcome of moderate, severe, and critical COVID-19 patients. Research over a longer period is also required to determine the development of the subject's condition and diagnosis.

CONCLUSION

Vaccination, especially the 2nd dose, was significantly associated with the cure rate of moderate to critically severe COVID-19 patients with hypertension and without comorbidities. Hence, it is important to diagnose controlled hypertension early. Diabetes is an independent risk factor for the prognosis of COVID-19. More attention should be paid to the prevention and treatment of diabetic patients, especially those who require insulin therapy. Further prospective research is needed on the type of COVID-19 vaccines to see the success rate of vaccination in people with comorbidities.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. Geneva; 2020 [cited 2021 Jan 31]. Available from: https://www.who.int/publications/i/item/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)
2. World Health Organization. Coronavirus Disease (COVID-19) Treatment Guidelines [Internet]. National Institutes of Health. 2020 [cited 2021 Jan 31]. Available from: https://www.covid19treatmentguidelines.nih.gov/
3. Hu Y, Sun J, Dai Z, Deng H, Li X, Huang Q, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Virol. 2020;127:104371.
4. Karyono DR, Wicaksana AL. Current prevalence, characteristics, and comorbidities of patients with COVID-19 in Indonesia. Journal of Community Empowerment for Health. 2020;3(2):77–84.
5. Del Sole F, Farcomeni A, Loffredo L, Carnevale R, Menichelli D, Vicario T, et al. Features of severe COVID-19: A systematic review and meta-analysis. Eur J Clin Invest. 2020;50(10):e13378.
6. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Emergence, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91–8.
7. Zheng C, Shao W, Chen X, Zhang B, Wang G, Zhang W. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. International Journal of Infectious Diseases. 2022;114:252–60.
8. Regev-Yochay G, Gonen T, Gilboa M, Mandelboim M, Indenbaum V, Amit S, et al. Efficacy of a fourth dose of Covid-19 mRNA vaccine against Omicron. N Engl J Med. 2022;386(14):1377–80.
9. Swamy S, Koch CA, Hannah-Shmouni F, Schiffrin EL, Klubo-Gwiezdzinska J, Gubbi S. Hypertension and COVID-19: Updates from the era of vaccines and variants. J Clin Transl Endocrinol. 2022;27:100285.
10. Sun SH, Chen Q, Gu HJ, Yang G, Wang YX, Huang XY, et al. A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host Microbe. 2020;28(1):124-133.e4.
11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.
13. Zhang X, Yu J, Pan L ya, Jiang H yin. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: A systematic review and meta-analysis. Pharmacol Res. 2020;158:104927.
14. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19–systematic review, meta-analysis, and meta-regression. Journal of Stroke and Cerebrovascular Diseases. 2020;29(8):104949.
15. Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ace-inhibitors and arbs in covid-19 patients. Elife. 2020; 9:e57278.
16. Singh AK, Gillies CL, Singh R, Singh A, Chudasama Y, Coles B, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. Diabetes Obes Metab. 2020;22(10):1915–24.
17. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736–41.
18. Rao S, Lau A, So HC. Exploring diseases/traits and blood proteins causally related to expression

of ACE2, the putative receptor of SARS-CoV-2: A mendelian randomization analysis highlights tentative relevance of diabetes-related traits. Diabetes Care. 2020;43(7):1416–26.

19. Fernandez C, Rysä J, Almgren P, Nilsson J, Engström G, Orho-Melander M, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. J Intern Med. 2018;284(4):377–87.
20. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nature Reviews Endocrinology 2020 17:1. 2020;17(1):11–30.
21. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5.
22. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, Felix SEB, et al. Coronavirus disease 2019 case surveillance — United States, January 22–May 30, 2020. Morbidity and Mortality Weekly Report. 2020;69(24):759–65.
23. Zhang ZL, Hou YL, Li DT, Li FZ. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scand J Clin Lab Invest. 2020;80(6):1–7.

Original Article

The Role of Chemotherapy Status, Absolute Lymphocyte Count and Neutrophil Lymphocyte Ratio as Biomarkers of Candidiasis in Lung Cancer Patients

Muhamad Yusuf Musthafa[1], Iin Noor Chozin[1], Ungky Agus Setyawan[1], Teguh Wahyu Sardjono[2], Noorhamdani AS[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya, dr. Saiful Anwar Hospital, Malang, Indonesia
[2]Department of Parasitology, Faculty of Medicine, Universitas Brawijaya, dr. Saiful Anwar Hospital, Malang, Indonesia
[3]Department of Microbiology, Faculty of Medicine, Universitas Brawijaya, dr. Saiful Anwar Hospital, Malang, Indonesia

Abstract

Background: Gradually, fungal infections are growing and have become a medical concern. Candida species are one of the most common pathogens in immunocompromised patients, such as those with lung cancer causing invasive fungal disease. Early diagnosis of candidiasis is critical for patient care in lung cancer patients. Anti-mannan IgM and IgG biomarkers are used to diagnose candidiasis. This study aims to determine the relationship between chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio to antimannan IgM and IgG.

Methods: A correlative analytic cross-sectional study was conducted on 37 lung cancer patients with positive candida sputum cultures in Dr. Saiful Anwar Malang Hospital. The 37 patients were examined for total lymphocyte level, neutrophil-lymphocyte ratio, anti-mannan IgM, and IgG. Data analysis used a contingency coefficient to determine the relationship between chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio to anti-mannan IgM and IgG.

Results: This study showed a positive correlation between chemotherapy status with anti-mannan IgM and IgG, although insignificant (P>0.05). However, there was a significant correlation between total lymphocytes and anti-mannan IgG (P=0.0001) and between neutrophil-lymphocyte ratio and antimannan IgM (P=0.004).

Conclusion: The study revealed that chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio could be a biomarker of candidiasis, so lung cancer patients with a history of chemotherapy, lymphopenia, and increased neutrophil-lymphocyte ratio should consider receiving antifungals earlier.

Keywords: antimannan antibodies, candidiasis, lung cancer

Corresponding Author:
Muhamad Yusuf Musthafa | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya, dr. Saiful Anwar Hospital, Malang, Indonesia | yusuf.musthafa.ym@gmail.com

Submitted: April 21st, 2021
Accepted: February 27th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 190–4
https://doi.org/10.36497/jri.v43i3.518

INTRODUCTION

Fungal infections are gradually increasing and have become a widespread concern in the medical world, where candida species are primary pathogens of invasive fungal diseases. More than 400,000 people annually experience life-threatening candida infections.[1] The incidence of pulmonary candidiasis varies and increases in patients with high risks such as malignancy, broad-spectrum antibiotics, chemotherapeutic agents, organ transplants, implanted invasive medical devices, and parenteral nutrition.[2]

Immune status in fighting candida infection is influenced by many factors, including age, underlying disease, chemotherapy status, lymphocyte count, neutrophil count, and others.[3] In lung cancer patients, immunosuppression and gastrointestinal mucosa disorders occur, which play an essential role in the risk of candidiasis.[4] Chemotherapy agents in cancer also cause a decrease in the function of the body's immune system through the release of calreticulin (CALR), chemokine ligand 10 (CXCL 10), high mobility group box 1 (HMGB1), and cell stress. This will trigger the process of apoptosis, autophagy, and disruption of T-cell priming.[5]

Lymphocytes and neutrophils play a role in the innate and adaptive immune system. Lymphocyte cells play an essential role in the production of T-cells

in cellular immunity and the production of B cells in humoral immunity. A decrease in the absolute number of lymphocytes that occurs in people with immunocompromised will reduce antigen presentation, thereby reducing immunoglobulin production.[3,4] Neutrophils are the first leukocytes to migrate from the blood to sites of injury or infection to kill pathogens and remove debris. An increase in the neutrophil-lymphocyte ratio indicates an inflammatory response in the body.[3]

The diagnosis of candidiasis is challenging because there are no specific clinical signs and symptoms. Early diagnosis of candida infection is essential in determining early management and management of patients to reduce mortality.[1] There are several non-culture biomarker tests in diagnosing candidiasis, one of which is the detection of anti-mannan antibodies against candida. The examination of anti-mannan IgM and IgG has a sensitivity of 40%-70% and a specificity of 50%-80%.[6]

This study aims to determine the correlation between chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio to anti-mannan IgM and IgG in immunocompromised patients such as lung cancer in terms of helping candidiasis management earlier.

METHODS

The method in this study used a cross-sectional design, where the data source was obtained from collecting lung cancer patients at Dr. Saiful Anwar Malang. Samples were obtained using consecutive sampling in the inpatient room of Dr. Saiful Anwar Malang Hospital. The inclusion criteria included inpatients aged >18 years with underlying lung cancer disease who had established pathological anatomy in both non-small lung cancer and small cell lung cancer and patients with candida infection as evidenced by positive candida sputum culture. The exclusion criteria in this study were all lung cancer patients with non-candidal sputum culture. The sample size used in this study was 37 patients who met the inclusion and exclusion criteria.

The operational standards at Dr. Saiful Anwar Malang Hospital carry out routine blood tests and candida sputum culture. Meanwhile, an anti-mannan IgM and IgG examination was conducted in the Physiological Laboratory of the Faculty of Medicine, University of Brawijaya, Malang using the Human Candida Albicans ELISA kit, BT-Lab brand. Data analysis used correlative analysis between Absolute Lymphocyte Ratio (ALC), Neutrophil Lymphocyte Ratio (NLR), and chemotherapy status with IgM and IgG anti mannan.

The statistical test uses a contingency coefficient where the value of $P<0.05$ with 95% CI. This research has received ethical approval from the health research ethics committee of Dr. Saiful Anwar Malang Hospital with number 400/205/K.3/302/2020.

RESULTS

The distribution of research data is shown in Table 1.

Table 1. Characteristics of Research Data

Characteristics	n	%
Gender		
Male	27	73.0
Female	10	27.0
Age		
18–45 years old	6	16.2
46–59 years old	16	43.2
60–74 years old	11	29.7
75–90 years old	4	10.8
Histopathological Distribution		
Adenocarcinoma	24	64.9
Squamous carcinoma	6	16.2
Adenosquamous carcinoma	3	8.1
Small cell carcinoma	3	8.1
Undifferentiated cell	1	2.7
Chemotherapy status		
Negative	18	48.6
Positive	19	51.4
Absolute lymphocyte count		
<1200 cell/µL	22	59.5
>1200 cell/µL	15	40.5
Neutrophil lymphocyte ratio		
>3.53	15	40.5
<3.53	22	59.5
Anti manan IgM antibodies		
Positive	22	59.5
Negative	15	40.5
Anti manan IgG antibodies		
Positive	5	13.5
Negative	32	85.5

The majority are male, as many as 27 people (73.0%), with the middle age range (46-59 years) having the most significant number of 16 people (43.2%). Based on the histopathological picture of lung cancer, the distribution of the study was bronchogenic, primarily adenocarcinoma in several 24 people (64.9%), while based on chemotherapy status, out of 37 study samples, 19 of them (51.4%) had undergone chemotherapy or received at least two cycles of chemotherapy. The rest, as many as 18 patients (48.6%), had never undergone chemotherapy.

Tables 2 and 3 describe the correlation analysis between Absolute lymphocyte count (ALC), Neutrophil lymphocyte ratio (NLR), and chemotherapy status for anti mannan IgM and IgG for candida. In this study, there was no significant correlation between ALC and anti-mannan IgM with a weak correlation strength (*P*=0.314; r=0.163), but there was a significant correlation with IgG with a robust correlation strength (*P*=0.314; r=0.613).

Table 2. ALC contingency coefficient test, NLR, chemotherapy status with IgM anti-mannan

Characteristics	IgM		r	*P*
	Positive	Negative		
Absolute lymphocyte count				
<1200 cell/µL	4 (80.0%)	18 (56.2%)	0.163	0.314
>1200 cell/µL	1 (20.0%)	14 (43.8%)		
Neutrophil lymphocyte ratio				
>3.53	5 (100.0%)	10 (31.3%)	0.432	0.004
<3.53	0 (0.0%)	22 (68.7%)		
Chemotherapy status				
Negative	3 (60.0%)	15 (46.9%)	0.089	0.585
Positive	2 (40.0%)	17 (53.1%)		

In the statistical test between NLR and IgM anti-mannan, there was a significant correlation with a moderate correlation strength (*P*=0.004; r=0.432), but no significant correlation was found with IgG anti-mannan with a weak correlation strength (*P*=0.156; r=0.227).

This study showed a statistically insignificant correlation between chemotherapy status and IgM anti-mannan with feeble strength (*P*=0.585; r=0.089). Besides, there was no statistically significant correlation with IgG anti-mannan with weak correlation strength (*P*=0.156; r=0.227).

Table 3. ALC contingency coefficient test, NLR, chemotherapy status with IgG anti-mannan

Characteristics	IgG		r	*P*
	Positive	Negative		
Absolute lymphocyte count				
<1200 cell/µL	20 (90.9%)	2 (13.3%)	0.613	0.0001
>1200 cell/µL	2 (9.1%)	13 (86.7)		
Neutrophil lymphocyte ratio				
>3.53	11 (50.0%)	4 (26.7%)	0.227	0.156
<3.53	11 (50.0%)	11 (73.7%)		
Chemotherapy status				
Negative	13 (59.1%)	5 (33.3%)	0.245	0.124
Positive	9 (40.9%)	10 (66.7)		

DISCUSSION

Lung cancer is histologically divided into two types, namely Non-Small Cell Lung Cancer (NSCLC) (85%) and Small Lung Cell Cancer (SCLC) (15%), where NSCLC is divided into adenocarcinoma (38.5%), squamous carcinoma (20%) and large cell carcinoma (2.9%). Epidemiology of lung cancer is expected in the male sex and over 40 years of age.[7] In lung cancer, there are disturbances in antigen recognition, the energy of cytotoxic T cells, and activation of inflammatory inhibitory cells. In addition, in lung cancer, there is also an increase in the number of neutrophils caused by the production of GM-CSF, G-CSF, IL-1, and IL-6.[8]

In this study, 37 patients were diagnosed with candidiasis based on clinical features and positive candida sputum culture. Some patients in this study have negative IgM and IgG anti mannan; we assume immunocompromised patients, such as lung cancer, cannot form an adequate immune system.

This study found a positive correlation between chemotherapy status and anti-mannan IgM and IgG, although it had a weak correlation strength. Traktama and Sufiawati, in their research, stated that chemotherapy in cancer patients was a predictor of the risk of candida Albicans infection.[9] In chemotherapy, immunogenic cell death occurs by releasing calreticulin, CXCL 10, HMGB1, and cell stress, thereby reducing the humoral immune response.[5] There was no significant correlation found in this study, which could be due to not considering the type of chemotherapy and how long the respondent received chemotherapy agents.

This study also found a positive correlation between ALC and anti-mannan IgM and IgG. Shimizu et al mentioned a negative correlation between lymphocyte levels and candida mannan serum levels. In another study, Koga et al showed that normal lymphocyte status would decrease serum levels of Human 1,3-β-D-Glucan by 0.015 pg/dl.[10]

IgM plays a role in inhibiting the adhesion and filamentation of candida yeast cells. In contrast, IgG anti-mannan plays a role in initiating the complement system and increasing phagocytosis. Lymphocyte cells play an essential role in the specific immune system, producing T cells and B cells in humoral immunity. A decrease in the total lymphocyte count will reduce antigen presentation so that immunoglobulin production decreases.[11]

This study positively correlates NLR and anti-mannan IgM and IgG. Meshall et al mentioned NLR as a prognostic factor for various infections (bacterial, fungal, and viral).[11] Neutrophils are the first leukocytes to migrate from the blood to sites of injury or infection. The increase in NLR is an inflammatory response due to the infection process. The presence of a fungal infection will initiate the formation of antibodies as a humoral immune response.[12]

LIMITATION

This study has some limitations, including not conducting a specific analysis of other candidiasis risk factors, not analyzing clinical data, radiological features, and lung cancer progression rates, and not analyzing chemotherapy history, duration, and chemotherapy agents.

CONCLUSION

This study concludes that chemotherapy status, absolute lymphocyte count, and neutrophil lymphocyte ratio play a role in influencing the formation of anti-mannan IgM and IgG against candidiasis. Patients with immunocompromise, such as lung cancer, who have undergone chemotherapy, lymphocytopenia, and increased NLR tend not to form anti-mannan antibodies, so it is recommended to be given antifungals earlier.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Li F, Yu X, Ye L, Zhou G, Wang L, Luo Y. Clinical value of (1,3)-β-D-glucan, mannan, antimannan IgG and IgM antibodies in diagnosis of invasive candidiasis. Med Mycol. 2019;57(8):976–86.
2. Pitarch A, Nombela C, Gil C. Diagnosis of invasive candidiasis: From gold standard methods to promising leading-edge technologies. Curr Top Med Chem. 2018;18(16):1375–92.
3. Netea MG, Joosten LAB, Van Der Meer JWM, Kullberg BJ, Van De Veerdonk FL. Immune defence against Candida fungal infections. Nature Reviews Immunology 2015 15:10. 2015;15(10):630–42.
4. Alves J, Palma P, Azevedo D, Rello J. Candidemia in the patient with malignancy. Hosp Pract (1995). 2018;46(5):246–52.
5. Gebremeskel S, Johnston B. Concepts and mechanisms underlying chemotherapy induced immunogenic cell death: impact on clinical studies and considerations for combined therapies. Oncotarget. 2015;6(39):41600–19.
6. Wang K, Luo Y, Zhang W, Xie S, Yan P, Liu Y, et al. Diagnostic value of Candida mannan antigen and anti-mannan IgG and IgM antibodies for Candida infection. Mycoses. 2020;63(2):181–8.
7. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 2011;32(4):605–44.
8. Pinzon-Charry A, Maxwell T, López JA. Dendritic cell dysfunction in cancer: a mechanism for

immunosuppression. Immunol Cell Biol. 2005;83(5):451–61.

9. Koga M, Koibuchi T, Kikuchi T, Nakamura H, Miura T, Iwamoto A, et al. Kinetics of serum β-D-glucan after Pneumocystis pneumonia treatment in patients with AIDS. Intern Med. 2011;50(13):1397–401.
10. Traktama DO, Sufiawati I. Keparahan mukositis oral pada pasien kanker kepala leher akibat kemoterapi dan/atau radioterapi. Majalah Kedokteran Gigi Indonesia. 2018;4(1):52–63.
11. Elluru SR, Kaveri S V., Bayry J. The protective role of immunoglobulins in fungal infections and inflammation. Semin Immunopathol. 2015;37(2):187–97.
12. Meshaal MS, Nagi A, Eldamaty A, Elnaggar W, Gaber M, Rizk H. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as independent predictors of outcome in infective endocarditis (IE). The Egyptian Heart Journal. 2019;71:13.

Original Article

Effectiveness of COVID-19 Antivirus Therapy and Its Relationship with Vaccination: A Retrospective Analysis

Andi Utari Prasetya Ningrum[1], Retnosari Andrajati[1,2], Nadia Farhanah Syafhan[1,2], Aditya Wirawan[3]

[1]Pharmacy Department, Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia
[2]Pharmaceutical Unit and Central Sterile Supply Department, Universitas Indonesia Hospital, Depok, Indonesia
[3]Department of Pulmonology and Respiratory Medicine, Universitas Indonesia Hospital, Depok, Indonesia

Abstract

Background: COVID-19 is known to have infected more than a million people. COVID-19 can be treated with antivirals. Besides antiviral drugs, vaccination becomes one of the strategies to suppress the spread of COVID-19. This study aimed to analyze the effectiveness of antivirus and the relationship between vaccination and the effectiveness of the two antiviral therapies in COVID-19 patients based on improvements in the patient's clinical condition, length of stay, and mortality.

Methods: This study used a retrospective cohort design conducted at the Universitas Indonesia Hospital, Depok, Indonesia. Data were taken from medical records and hospital databases from January 2021 to August 2022. The antivirals in this study were remdesivir and favipiravir. The samples were divided into two groups, namely the vaccinated and unvaccinated groups.

Results: The factor affecting the effectiveness of remdesivir and favipiravir therapy was the severity of COVID-19. It was shown that vaccination had a significant effect on improving clinical conditions, reducing length of stay, and reducing mortality in patients treated with remdesivir who had been vaccinated compared to those who had not been vaccinated. In patients who received favipiravir therapy and were vaccinated, it also showed an effect on improving clinical conditions, length of stay, and mortality compared to patients who were not vaccinated, although the results were not statistically significant.

Conclusion: Vaccination had a positive effect on the effectiveness of remdesivir and favipiravir in COVID-19 patients, which could improve the patient's clinical condition in a better direction, as well as reduce the length of hospitalization and mortality.

Keywords: COVID-19, effectiveness, favipiravir, remdesivir, vaccination

Corresponding Author:
Retnosari Andrajati | Pharmacy Department, Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia | andrajati@farmasi.ui.ac.id

Submitted: January 18th, 2021
Accepted: January 23rd, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 195–203
https://doi.org/10.36497/jri.v43i3.434

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has rapidly spread as a pandemic and has infected more than 1 million people worldwide.[1] The clinical manifestations of COVID-19 are broad and can range from mild to critical illness.[2] Common symptoms include fever, cough, shortness of breath, anosmia, headache, skin symptoms, and others. Such clinical manifestations can be critical in some patients with other diseases and the elderly.[3] Thus, comprehensive steps must be taken to resolve the pandemic optimally, starting from preventive to curative measures. Improper treatment should be addressed to help reduce infection cases and death.[4]

Several potential antivirals drugs that can be used to treat COVID-19 have been tested and recommended in several countries, including Indonesia.[5] Remdesivir is a nucleoside analog that is known to inhibit the replication of SARS-CoV-2.[6] Data on the effectiveness of remdesivir are varied. A retrospective study of health systems showed that remdesivir reduced hospital stay and indicated good clinical improvement in 342 recipients but did not reduce mortality.[7] However, another retrospective study of 28,555 patients showed a decrease in mortality at days 14 and 28.[8]

Meanwhile, favipiravir is an oral drug with a broad spectrum.[3] Data on the effectiveness of favipiravir are limited. A randomized control trial (RCT) study obtained that the combination of favipiravir and interferon-alfa treated SARS-CoV-2 infection more quickly than other combination therapies.[9] Another open-label study using a prospective RCT design found no significant difference in clinical recovery rates at day 7.[10]

Besides antiviral drugs, vaccination becomes one of the strategies used to suppress the spread of COVID-19. Vaccination is known to significantly reduce symptoms of COVID-19 in elderly patients and increase protection against serious illness.[11] Vaccines are known to reduce disease severity, length of stay, and mortality.[12]

Moreover, vaccination provides a significant reduction in the mean length of stay, ICU needs, mortality, and medical costs of patients compared to those who are not vaccinated.[13] Although it has many benefits, it turns out that there are still cases of post-vaccination COVID-19 infection, especially in Indonesia.[14,15] This has resulted in various perceptions in the community regarding the COVID-19 vaccine.

For drugs that are used in a pandemic era, monitoring the effectiveness of the therapy is important.[16] The effectiveness of remdesivir and favipiravir has been studied both in Indonesia and in other countries. However, the effect of vaccination on the effectiveness of these two drugs in COVID-19 patients has not been proven.

Therefore, this study aimed to analyze the effectiveness of remdesivir and favipiravir, also the relationship between vaccination and the effectiveness of both antiviral therapies in COVID-19 patients based on improvements in the patient's clinical condition, length of stay, and mortality at the University of Indonesia Hospital, Depok, Indonesia.

METHODS

This observational study used a retrospective cohort design and was conducted at the University of Indonesia Hospital, Depok, Indonesia. The effectiveness of remdesivir and favipiravir therapy was assessed based on clinical improvement using the WHO clinical progression score, covering a scale of 0 (not infected) to 10 (dead), length of stay, and mortality. The ethical approval of this study was obtained from the Ethics Committee of the Universitas Indonesia Hospital (number: S-037/KETLIT/RSUI/VIII/2022).

The population of this study consisted of inpatients at the Universitas Indonesia Hospital who had confirmed COVID-19. Inclusion criteria for this study were patients over 18 years of age with mild, moderate, or critical severity, patients with and without comorbidities, and patients taking remdesivir and favipiravir therapy. This study excluded patients with incomplete medical record data, patients who had changed or used two antivirals during treatment, patients who were discharged at their request, and patients who were referred to another hospital. The minimum sample for each group is 45 subjects. The determination of the sample used consecutive sampling.

In this study, comparisons were made by assessing the vaccine (patients receiving COVID-19 vaccination) and non-vaccine (patients who have not received COVID-19 vaccination) groups based on the value of clinical improvement, length of stay, and mortality numbers. Improvement in the patient's clinical condition 14 days after the therapy was based on the WHO clinical progression score.[17,18] It is said that there is an improvement if there is a decrease in the score of at least 2 after 14 days of therapy.[7]

This clinical condition assessment was based on the doctor's assessment recorded in the medical record. The endpoint of the observation was the 14th day after antiviral therapy, calculated starting from the first day of the administration of the therapy to patients. The length of stay was the number of days the patient was hospitalized, which was calculated from the first day of admission to the hospital until the day the patient was discharged. Mortality was assessed based on the patient's condition when discharged from the hospital, whether alive or dead.

This study categorized age according to WHO groups. The research subjects were adults (≥18 years) and elderly patients (>59 years), which was an age group that was at risk of having a worsening condition due to COVID-19[19] and associated with low immune function and increased mortality.[20] Meanwhile, gender was categorized into male and female. Comorbidities were divided into no comorbidities and comorbidities, as comorbidities were associated with lower immune function,[20] higher severity, and higher mortality in COVID-19 patients.[21] The body mass index (BMI) category was classified

into underweight-normal (<18.5 to ≤24.9) and overweight-obese (25 to ≥30).[20,22] The severity categories were based on the 4th edition of the COVID-19 management guidelines: mild, moderate, and severe/critical.[23] All covariates were thought to be confounding variables for improvement in clinical condition, length of stay, and mortality.

Data were taken from medical records and hospital databases from January 2021 to August 2022. Data covered demographics, co-morbidities, history of antiviral therapy (type of antiviral and time of antiviral administration), vaccination status (already vaccinated against COVID-19 or not), clinical results (patient's condition 14 days after the therapy), and polymerase chain reaction (PCR) test results.

Data analysis used the statistical software IBM SPSS, version 23. Data were analyzed using descriptive analysis to describe patient demographic information and the patient's clinical condition status. Categorical data were presented as proportions (%), and numerical data were presented as mean±SD. Bivariate analysis was used by applying the Chi-square test to analyze the effect of vaccination and other variables on improving the patient's clinical condition, length of stay, and mortality of patients receiving remdesivir or favipiravir.

RESULTS

This study evaluated a total of 275 medical records of patients receiving remdesivir. This number consisted of two groups: vaccine groups (105 patients) and non-vaccine groups (170 patients) who met the predetermined criteria. The mean age of the patients was 56.01±15.68. Most of the patients in both groups were adults, had a history of co-morbidities, and had more than one co-morbidity (Table 1).

The mean body mass index (BMI) was 25.71±6.10. In the vaccine group, the majority were female patients (50.5%) with the BMI category of <18.5 to <24.9 (thin to normal), for a total of 55 patients (52.4%). Then, the degree of disease severity was mild or moderate (79.0%). Meanwhile, in the non-vaccine group, the majority were male patients (54.1%), with the highest BMI categories of overweight to obesity, with a total of 86 patients (50.6%) and a severe or critical degree of severity (74.7%) (Table 1).

This study evaluated a total of 133 patients receiving favipiravir therapy. This number consisted of vaccine groups (47 patients who had been vaccinated) and non-vaccine groups (86 patients who had not been vaccinated).

Table 1. Characteristics of COVID-19 patients receiving remdesivir and favipiravir theraphy based on vaccination status

Patient characteristics	Remdesivir		Favipiravir	
	Vaccine (n=105)	Non vaccine (n=170)	Vaccine (n=47)	Non vaccine (n=86)
Age (mean±SD)	56.01±15.68		49.33±16.72	
Adult (18-59 years)	65 (61.9%)	92 (54.1%)	37 (78.7%)	59 (68.6%)
Elderly (>59 years)	40 (38.1%)	78 (45.9%)	10 (21.3%)	27 (31.4%)
Gender				
Male	52 (49.5%)	92 (54.1%)	17 (36.2%)	38 (44.2%)
Female	53 (50.5%)	78 (45.9%)	30 (63.8%)	48 (55.8%)
History of comorbidities				
No	14 (13.3%)	15 (8.8%)	10 (21.3%)	25 (29.1%)
Yes	91 (86.7%)	155 (91.2%)	37 (78.7%)	61 (70.9%)
Number of comorbidities				
None	14 (13.3%)	15 (8.8%)	10 (21.3%)	25 (29.1%)
1 Comorbidity	23 (21.9%)	25 (14.7%)	14 (29.8%)	26 (30.2%)
>1 Comorbidities	68 (64.8%)	130 (76.5%)	23 (48.9%)	35 (40.7%)
Body mass index (mean±SD)	25.71±6.10		25.77±5.47	
Thin-Normal	55 (52.4%)	84 (49.4%)	28 (59.6%)	35 (40.7%)
Overweight-Obese	50 (47.6%)	86 (50.6%)	19 (40.4%)	51 (59.3%)
Degree of severity				
Mild/Moderate	83 (79.0%)	43 (25.3%)	46 (97.9%)	85 (98.8%)
Severe/Critical	22 (21.0%)	127 (74.7%)	1 (2.1%)	1 (1.2%)

Table 2. The relationship between vaccination and the effectiveness of remdesivir and favipiravir therapy

Outcome	Remdesivir			Favipiravir		
	Vaccine (n=105)	Non vaccine (n=170)	*P*`	Vaccine (n=47)	Non vaccine (n=86)	*P*
Clinical condition improvement						
Improve	94 (89.5%)	91 (53.5%)	0.0001*	46 (97.9%)	78 (90.7%)	0.158
Worsen	11 (10.5%)	79 (46.5%)		1 (2.1%)	8 (9.3%)	
Length of stay						
1–14 days	90 (85.7%)	101 (59.4%)	0.0001*	45 (95.7%)	81 (94.2%)	1.000
>14 days	15 (14.3%)	69 (40.6%)		2 (4.3%)	5 (5.8%)	
Mortality						
No	95 (90.5%)	114 (67.1%)	0.0001*	46 (97.9%)	83 (96.5%)	1.000
Yes	10 (9.5%)	56 (32.9%)		1 (2.1%)	3 (3.5%)	

Note: *significant *P*<0.05

In general, the characteristics of the patients were quite similar for the vaccine and non-vaccine groups. Most of the patients in both groups were female, adult patients with an mean age of 49.33±16.72 had a history of comorbidities, had more than 1 comorbidity with mild/moderate severity, and had an mean BMI of 25.77±5.47. In the vaccine group, most of the patients had a thin to normal BMI of 28 (59.6%), while the majority in the non-vaccine group had an overweight to obese BMI of 151 (59.3%) (Table 1).

The assessment of the effectiveness of therapy is based on the clinical condition improvement, length of stay, and mortality of COVID-19 patients. A total of 89.5% of patients who were treated with remdesivir in the vaccine group experienced an improvement in their clinical condition compared to those in the non-vaccine group (OR=0.135; 95% CI=0.067-0.270; *P*=0.0001). Then, as many as 85.7% of patients receiving remdesivir therapy in the vaccine group had a length of stay of 1–14 days, while 59.4% of those in the non-vaccine group had a length of stay 1–14 days (OR=0.244; 95% CI=0.130-0.456; *P*=0.0001) (Table 2).

In terms of the mortality parameter, 90.5% of patients receiving remdesivir therapy in the vaccine group did not die compared to the non-vaccine group (OR=0.214; 95% CI=0.101-0.443; *P*=0.0001). Among patients who were given favipiravir therapy, it was found that 97.9% of patients in the vaccine group experienced better clinical conditions than those in the non-vaccine group, but this was not statistically significant (OR=0.212; 95% CI=0.026-1.749; *P*=0.158). In terms of the length of stay, the results showed that 95.7% of patients in the vaccine group had a length of stay of 1-14 days, while 4.3% of the patients in the non-vaccine group had a length of stay of <14 days, but it was not statistically significant (OR=0.720; 95% CI=0.134-3.863; *P*=1.000). For the mortality parameter, 97.9% of patients in the vaccine group did not die even though it was not statistically significant (OR=0.601; 95% CI=0.061-5.949; *P*=1.000) (Table 2).

In this study, it was also observed that the severity of COVID-19 was a risk factor that significantly influenced the clinical condition improvement of COVID-19 patients who were given remdesivir therapy (*P*<0.05), which was 87.3% of patients with mild severity were experiencing better clinical condition improvement, and as many as 50.3% of patients with severe or critical severity had improved clinical condition (OR=0.147; 95% CI=0.080-0.273; *P*=0.0001). On the length of stay parameter, gender (OR=0.572; 95% CI=0.339-0.966; *P*=0.037) and the degree of COVID-19 severity (OR=0.087; 95% CI=0.042-0.180; *P*=0.0001) were risk factors that significantly affected the length of stay of COVID-19 patients who were given remdesivir therapy with *P*<0.05 (Table 3).

In terms of the mortality parameter, it was obtained that age, comorbidities, and disease severity were risk factors that significantly affected mortality in COVID-19 patients who were given remdesivir therapy (*P*<0.05). About 81.5% of adult patients (OR=2.016; 95% CI=1.152-3.530; *P*=0.015), 100% of patients with no comorbidities, and 88.9% of patients with mild or moderate severity (OR=0.233;

95% CI=0.122-0.447; *P*=0.0001) did not experience mortality.

The risk factor that significantly affected the clinical condition improvement of patients receiving favipiravir therapy was the degree of severity (*P*<0.05), with as many as 94.7% of mild/moderate severity patients experiencing an improvement in clinical conditions in a better direction; while among those with severe/critical severity, there were no patients who experienced an improvement in clinical conditions. There were no risk factors that significantly affected the length of stay of COVID-19 patients receiving favipiravir. The risk factor for disease severity was a factor that significantly affects mortality in COVID-19 patients receiving favipiravir therapy with *P*<0.05. It is known that 98.5% of patients with mild/moderate severity do not experience mortality (Table 4).

DISCUSSION

This study showed that the patient's vaccination status affected the increase in the effectiveness of remdesivir and favipiravir therapy. The COVID-19 patients receiving remdesivir therapy in the vaccine groups showed that the improvement in their clinical condition increased compared to those in the non-vaccine group (89.5% vs 53.35%).[24,25]

Table 3. Factors affecting the effectiveness of remdesivir therapy

Risk Factor	Clinical condition improvement			Length of stay			Mortality		
	Improve	Worsen	*P*	1-14 days	>14 days	*P*	No	Yes	*P*
Age									
Adult (18–59 years)	109 (69.4%)	48 (30.6%)	0.436	108 (68.8%)	49 (31.2%)	0.793	128 (81.5%)	29 (18.5%)	0.015*
Elderly (>59 years)	76 (64.4%)	42 (35.6%)		83 (70.3%)	35 (29.7%)		81 (68.6%)	37 (31.4%)	
Gender									
Male	89 (61.8%)	55 (38.2%)	0.053	92 (63.9%)	52 (36.1%)	0,037*	104 (72.2%)	40 (27.8%)	0.157
Female	96 (73.3%)	35 (26.7%)		99 (75.6%)	32 (24.4%)		105 (80.2%)	26 (19.8%)	
Comorbidity									
No	23 (79.3%)	6 (20.7%)	0.208	21 (72.4%)	8 (27.6%)	0.833	29 (100.0%)	0 (0.0%)	0.0001*
Yes	162 (65.9%)	84 (34.1%)		170 (69.1%)	76 (30.9%)		180 (73.2%)	66 (26.8%)	
BMI									
Thin-Normal	96 (69.1%)	43 (30.9%)	0.607	101 (72.7%)	38 (27.3%)	0.295	109 (78.4%)	30 (21.6%)	0.397
Overweight-Obese	89 (65.4%)	47 (34.6%)		90 (66.2%)	46 (33.8%)		100 (73.5%)	36 (26.5%)	
Degree of severity									
Mild/Moderate	110 (87.3%)	16 (12.7%)	0.0001*	116 (92.1%)	10 (7.9%)	0.0001*	112 (88.9%)	14 (11.1%)	0.0001*
Severe/Critical	75 (50.3%)	74 (49.7%)		75 (50.3%)	74 (49.7%)		97 (65.1%)	52 (34.9%)	

Note: *significant *P*<0.05

Table 4. Factors affecting the effectiveness of favipiravir therapy

Risk Factor	Clinical condition improvement			Length of stay			Mortality		
	Improve	Worsen	*P*	1-14 days	>14 days	*P*	No	Yes	*P*
Age									
Adult (18–59 years)	92 (95.8%)	4 (4.2%)	0.115	93 (96.9%)	3 (3.1%)	0.094	95 (99.0%)	1 (1.0%)	0.065
Elderly (>59 years)	32 (86.5%)	5 (13.5%)		33 (89.2%)	4 (10.8%)		34 (91.9%)	3 (8.1%)	
Gender									
Male	51 (92.7%)	4 (7.3%)	1.000	51 (92.7%)	4 (7.3%)	0.447	53 (96.4%)	2 (3.6%)	1.000
Female	73 (93.6%)	5 (6.4%)		75 (96.2%)	3 (3.8%)		76 (97.4%)	2 (2.6%)	
Comorbidity									
No	34 (97.1%)	1 (2.9%)	0.444	34 (97.1%)	1 (2.9%)	0.675	35 (100.0%)	0 (0.0%)	0.573
Yes	90 (91.8%)	8 (8.2%)		92 (93.9%)	6 (6.1%)		94 (95.9%)	4 (4.1%)	
BMI									
Thin-Normal	59 (93.7%)	4 (6.3%)	1.000	60 (95.2%)	3 (4.8%)	1.000	62 (98.4%)	1 (1.6%)	0.621
Overweight-Obese	65 (92.9%)	5 (7.1%)		66 (94.3%)	4 (5.7%)		67 (95.7%)	3 (4.3%)	
Degree of severity									
Mild/Moderate	124 (94.7%)	7 (5.3%)	0.004*	125 (95.4%)	6 (4.6%)	0.103	129 (98.5%)	2 (1.5%)	0.001*
Severe/Critical	0 (0.0%)	2 (100.0%)		1 (50.0%)	1 (50.0%)		0 (0.0%)	2 (100.0%)	

Note: *significant *P*<0.05

Meanwhile, patients receiving favipiravir therapy in the vaccine group indicated good clinical condition improvement compared to those in the non-vaccine group (97.9% vs 90.7%) although not statistically significant. This is compatible with previous studies, which obtained that vaccination and antivirals had a synergistic effect, and also that vaccination and administration of remdesivir in high-risk patients could prevent the clinical development of COVID-19 towards a more severe one. [24,25]

Another study found that the use of remdesivir revealed good improvement in clinical conditions.[7] There was also a study that indicated that favipiravir therapy could increase clinical improvement on days 7 and 14, but this was not statistically significant.[9] Remdesivir and favipiravir are RNA-dependent RNA polymerase (RdRP) inhibitors that are predicted to be able to treat severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[3,26] The clinical condition improvement of the patient was assessed when antiviral therapy was first given for up to 14 days using the WHO clinical progression score. If there is a decrease in the score of at least 2 after 14 days of therapy, it is considered that there is clinical improvement.

This present study discovered that the degree of severity affected improvement in clinical conditions, length of stay, and mortality. This is in line with previous studies which stated that severity could affect the patient's recovery process.[27] Generally, the severity of COVID-19 is associated with the systemic inflammation experienced by patients, which can increase the risk of mortality.[28] Patients with mild COVID-19 have better clinical condition improvement, shorter lengths of stay, and a lower risk of mortality. This result is associated with the infection process of SARS-CoV-2; when the virus is still in the replication stage, it is expected that the use of antivirals will be more effective.[29]

Remdesivir and favipiravir act by inhibiting viral RdRp which then reduces viral replication rates.[30] Reduced viral load and a good immune response mean that there is no inflammatory response in the body, which leads to clinical condition improvement. The severity of COVID-19 is associated with an increase in the inflammatory reaction.[4]

The results of this study also noticed that the patient's vaccination status affected the reduction in length of stay and mortality in COVID-19 patients receiving remdesivir or favipiravir therapy. The majority of patients receiving remdesivir therapy in the vaccine group had a relatively shorter length of stay between 1 and 14 days (85.7% vs 59.4%) compared to those in the non-vaccine group (9.5% vs 32.9%) and also had a lower risk of mortality compared to patients who had not been vaccinated (9.5% vs 32.9%). Moreover, patients receiving favipiravir therapy in the vaccine group had a shorter length of stay between 1 and 14 days (95.7% vs 94.2%) and lower mortality (2.1% vs 3.5%) than those in the non-vaccine group, but this was not statistically significant. [24,25]

This result is consistent with previous studies showing that antiviral treatment combined with vaccination could be a strategic tool that significantly reduced the length of stay and mortality, and it was also pointed out that vaccination plus remdesivir administration reduced hospitalization time, and no intubation or death was reported. [24,25] Besides, other studies revealed that vaccination reduced the length of stay and mortality in COVID-19 patients.[12,13]

This study also observed that vaccination can reduce the severity of disease in COVID-19 patients who had been vaccinated compared to those who had not been vaccinated. This is in line with a study from Muhammed et al., which reported that vaccines reduced the incidence of infection and disease severity.[12]

The main results of this study were that the vaccination had a good effect on the effectiveness of remdesivir and favipiravir therapy in patients with COVID-19, and there was a synergistic relationship between vaccination and antiviral treatment for clinical condition improvement and reduced length of stay, especially for severe to critical cases. This study can also be used as a reference in helping to formulate treatment guidelines, particularly for the Indonesian population to reduce the burden on public health. It is expected that it can increase public

interest and awareness of vaccination. This study is helping to formulate the treatment.

LIMITATION

As this study was only conducted in one hospital, the results cannot be generalized. However, this study can describe the vaccination effect on the effectiveness of remdesivir and favipiravir therapy in COVID-19 patients at the Universitas Indonesia Hospital, Depok, Indonesia. Moreover, the limited number of samples also affects the results obtained. Further studies can be carried out prospectively in more than one location and consider some other variables.

CONCLUSION

It can be concluded that the degree of COVID-19 severity is a risk factor that can affect the effectiveness of COVID-19 antiviral therapy. Vaccination has a positive effect on the effectiveness of remdesivir and favipiravir therapy in patients with COVID-19. In this case, vaccination and antiviral therapy can improve the clinical condition of patients, reduce the length of stay and mortality, as well as reduce the severity of the disease. Besides, remdesivir and favipiravir can be the right treatment alternatives to cure COVID-19 patients.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCE

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
2. Handayani D, Hadi DR, Isbaniah F, Burhan E, Agustin H. Penyakit virus corona 2019. J Respir Indones. 2020;40(2):119–29.
3. Alamer A, Alrashed AA, Alfaifi M, Alosaimi B, AlHassar F, Almutairi M, et al. Effectiveness and safety of favipiravir compared to supportive care in moderately to critically ill COVID-19 patients: a retrospective study with propensity score matching sensitivity analysis. Curr Med Res Opin. 2021;37(7):1085–97.
4. Damayanti H, Sajinadiyasa IGK, Risni HW, Sauriasari R. The Effectiveness and Safety of Favipiravir in COVID-19 Hospitalized Patients at Tertiary Referral Hospital, Bali, Indonesia. Kesmas. 2021;16(4):289–97.
5. PDPI, PERKI, PAPDI, PERDATIN, IDAI. Pedoman tatalaksana COVID-19: Edisi 4. Indonesia: 4; 2022.
6. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020;383(19):1813–26.
7. Garibaldi BT, Wang K, Robinson ML, Zeger SL, Bandeen-Roche K, Wang MC, et al. Comparison of Time to Clinical Improvement with vs without Remdesivir Treatment in Hospitalized Patients with COVID-19. JAMA Netw Open. 2021;4(3):1–14.
8. Mozaffari E, Chandak A, Zhang Z, Liang S, Thrun M, Gottlieb RL, et al. Remdesivir treatment in hospitalized patients with COVID-19: a comparative analysis of in-hospital all-cause mortality in a large multi-center observational cohort. Clini Infect Dis. 2021;2019.
9. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020;6(10):1192–8.
10. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir Versus Arbidol for Clinical Recovery Rate in Moderate and Severe Adult COVID-19 Patients: A Prospective, Multicenter, Open-Label, Randomized Controlled Clinical Trial. Front Pharmacol. 2021;12:1–11.

11. Bernal JL, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. The BMJ. 2021;373.
12. Mohammed I, Nauman A, Paul P, Ganesan S, Chen KH, Jalil SMS, et al. The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. Hum Vaccin Immunother. 2022;18(1).
13. Ramakrishnan M, Prakash S, Nagar J. Impact of vaccination in reducing hospital expenses, mortality and mean length of stay among COVID-19 patients – A retrospective cohort study from India. medRxiv. 2021;
14. Soegiarto G, Purnomosari D, Wulandari L, Mahdi A, Fahmita D, Hadmoko T. Articles Incidence of SARS-CoV-2 infection in hospital workers before and after vaccination programme in East Java , Indonesia – A retrospective cohort study. The Lancet Reg Health - Southeast Asia. 2023;10:100130.
15. Cucunawangsih C, Wijaya RS, Lugito NPH, Suriapranata I. Post-vaccination cases of COVID-19 among healthcare workers at Siloam Teaching Hospital, Indonesia. Int J Infect Dis. 2021;107:268–70.
16. BPOM, JICA. Modul farmakovigilans untuk tenaga profesional kesehatan, proyek “ensuring drug and food safety.” Jakarta: Badan Pengawas Obat dan Makanan; 2020.
17. Marshall JC, Murthy S, Diaz J, Adhikari N, Angus DC, Arabi YM, et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20(8):e192–7.
18. Olender SA, Perez KK, Go AS, Balani B, Price-Haywood EG, Shah NS, et al. Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care. Clin Infect Dis. 2021;73(11):E4166–74.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62.
20. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507–13.
21. Hafiz M, Icksan AG, Harlivasari AD, Aulia R, Susanti F, Eldinia L. Clinical, radiological features and outcome of COVID-19 patients in a secondary Hospital in Jakarta, Indonesia. J Infect Dev Ctries. 2020;14(7):750–7.
22. Pranata R, Lim MA, Yonas E, Vania R, Lukito AA, Siswanto BB, et al. Body mass index and outcome in patients with COVID-19: A dose–response meta-analysis. Diabetes Metab. 2021;47(2):101178.
23. Kementerian PPN, Bappenas. Buku studi pembelajaran penanganan COVID-19 Indonesia. Jakarta, Bappenas; 2021.
24. Matrajt L, Brown ER, Cohen MS, Dimitrov D, Janes H. Could widespread use of antiviral treatment curb the COVID-19 pandemic? A modeling study. BMC Infect Dis. 2022;22(1):1–16.
25. Panagopoulos P, Petrakis V, Trypsianis G, Papazoglou D. Early 3-day course of remdesivir in vaccinated outpatients with SARS-CoV-2 infection. A success story. J Chemo. 2022;34(8):550–3.
26. Instiaty, Sri Darmayani IGAAP, Marzuki JE, Angelia F, William, Siane A, et al. Antiviral treatment of covid-19: A clinical pharmacology narrative review. Med J Indones. 2020;29(3):332–45.
27. Tan L, Kang X, Ji X, Li G, Wang Q, Li Y, et al. Validation of Predictors of Disease Severity and Outcomes in COVID-19 Patients: A Descriptive and Retrospective Study. Med. 2020;1(1):128-138.e3.
28. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting disease severity and outcome in COVID-19

patients: A review of multiple biomarkers. Arch Pathol Lab Med. 2020;144(12):1465–74.

29. Goyal A, Cardozo-Ojeda EF, Schiffer JT. Potency and timing of antiviral therapy as determinants of duration of SARS-CoV-2 shedding and intensity of inflammatory response. Sci Adv. 2020;6(47):1–13.
30. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;323(18):1824–36.

Original Article

Correlation of Smoking with Carbon Monoxide Level and Peak Expiratory Flow Rate in High School Students Banda Aceh

Julie Amalliah, Sri Dianova, Ferry Dwi Kurniawan, Teuku Zulfikar, Nurrahmah Yusuf

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia

Abstract

Background: Indonesia has the highest number of adolescent smokers in the world. Carbon monoxide (CO) is a by-product of tobacco smoking and is inhaled into the lungs. A smokerlyzer can monitor its level. Cigarette smoke also causes inflammation that affects airflow in the airways and can be detected by measuring the peak expiratory flow rate (PEFR). This study aims to determine the relationship between smoking and CO levels and PEFR in high school students in Banda Aceh City.

Methods: This quantitative study uses an analytical observational approach with a cross-sectional design. This study involved 300 students from five senior high schools in Banda Aceh. The data were analyzed using the Mann-Whitney and Spearman correlation with a significance value $P<0.05$.

Results: CO levels of the smoker students were higher (12.61±3.342 ppm) than nonsmoker students (2.46±0.569 ppm), $P=0.0001$. The mean PEFR for smoking students was lower than nonsmokers (61.11±9.163%) than for non-smoking students (78.48±6.804 %), $P=0.0001$. Duration of smoking in smoking students was also strongly associated with CO levels (r=0.749; $P=0.0001$) and PEFR (r= -0.560; $P=0.0001$).

Conclusion: There is a relationship between smoking and CO levels and PEFR in senior high school students in Banda Aceh.

Keywords: Banda Aceh, CO levels, PEFR, senior high school student, smoker student

Corresponding Author:
Ferry Dwi Kurniawan | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia | ferrydwikurniawan@unsyiah.ac.id

Submitted: November 25th, 2021
Accepted: March 28th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 204–9
https://doi.org/10.36497/jri.v43i3.294

INTRODUCTION

Worldwide, smoking is the most common cause of preventable death.[1] Based on a World Health Organization (WHO) report, 1 billion active smokers worldwide consume about 6 trillion cigarettes annually.[2] Six percent cause of death in women and 12% the cause of death in men are the results of tobacco use and exposure to cigarette smoke.[2]

The analysis of Baseline Health research in Indonesia year 2013 showed that the proportion of people who smoked every day from 2007 to 2013 slightly increased (23.7–24.3%).[3] In 2014, the Global Youth Tobacco Survey (GYTS) found that Indonesia has the highest number of adolescent smokers worldwide.[4] The main findings of GYTS in 2019 were that 19.2% of students, 38.3% of boys, and 2.4% of girls currently smoke cigarettes. Up to 57.8% of students were exposed to tobacco smoke at home, and 66.2% smoke inside an enclosed public place.[5]

Aceh is one of Indonesia's provinces with the highest smoking rate. The proportion of smokers in Aceh is 29.3% or 25% active smokers, 4.3% light smokers, 2.5% former smokers, and 6.2% nonsmokers. Baseline Health research in Indonesia year 2013 reported that the prevalence of smokers in Aceh province for the ≥10-years-old population, according to smoking habits, that is, daily smokers up to 25% and occasional smokers up to 4.3%, with an mean number of cigarettes smokers at age ≥10 years in Aceh are 15.3 rods. Even Aceh is included in the province, with a high percentage of smokers who start smoking at 15 to 19 years old.[3]

Smoking is one of the significant resources of carbon monoxide (CO). The body will absorb Carbon monoxide through the lung when inhaling cigarette smoke. CO infiltrates the blood vessels through the lung and then bindings with hemoglobin in the blood to form carboxyhemoglobin (COHb). Furthermore, the CO in the blood will re-enter the alveolus due to

the concentration gradient so that the CO will come out along with the exhaled air. The levels of CO at the time of expiration can be measured to determine a person's smoking status. Many researchers used CO measurements to determine tobacco exposure among cigarette smokers since measuring CO level is a simple and noninvasive procedure.[6]

Cigarette smoke increases inflammation by increasing the production of pro-inflammatory cytokines and accumulating immune cells within the respiratory tract.[7] The chronic inflammatory process in the respiratory tract will disturb the airflow, which leads to decreased lung function in smokers. When assessing lung function, three parameters are commonly used: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the peak expiratory flow rate (PEFR). Based on studies on smokers, the value of FVC, FEV_1, and PEFR is lower than nonsmokers.[8]

This study aimed to determine the relationship between smoking and CO levels and PEFR values in Banda Aceh City high school smokers and the relationship between smoking duration and CO levels and PEFR values.

METHODS

This type of research is a study with a cross-sectional design. The research was conducted from April to October 2021 in five high schools or the equivalent in Banda Aceh City. School selection is performed using simple random sampling techniques. At each school that has been determined, students are selected using a random sampling technique, where the researcher determines the number of students from every school, as many as 60 people, who meet the inclusion and exclusion criteria so that they can represent the population.

The inclusion criteria for this study were male students in grades 10, 11, and 12 at the upper secondary level or equivalent, aged 16–18 years, and willing to participate. Exclusion criteria were students with asthma, heart disease, or other congenital diseases and students absent on the day of measurement due to illness or permission.

Eligible samples complete a basic questionnaire containing students' personal information and smoking status. CO levels were measured using a CO smokerlyzer, while PEFR values were measured using a peak flow meter.

Statistical analysis was performed to examine the relationship between smoking and CO levels and PEFR values using the Mann-Whitney test. Spearman correlation the relationship between smoking duration with CO levels and PEFR values. Relationships were considered significant if $P<0.05$.

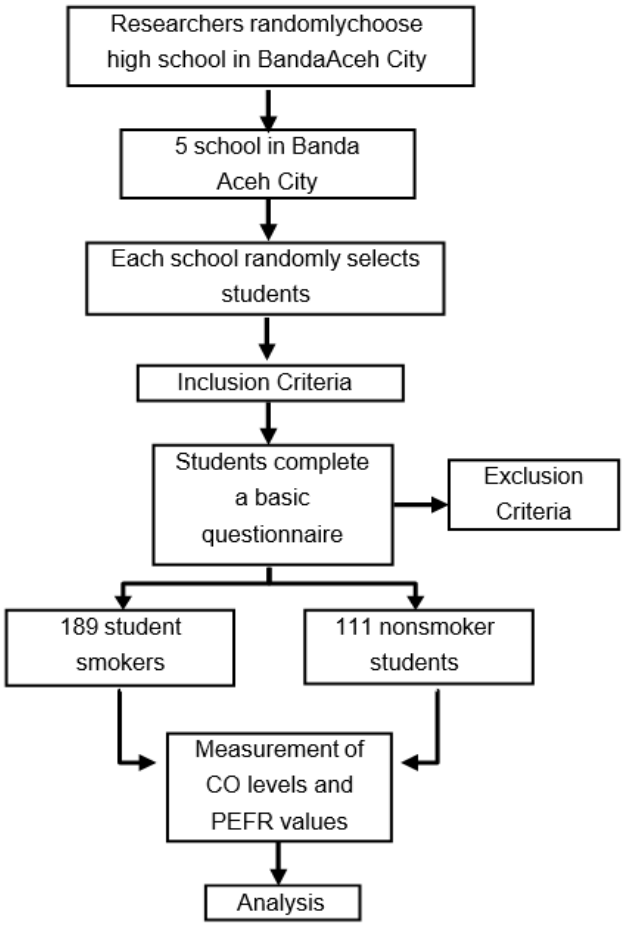

Figure 1. Research flow chart.

RESULTS

According to the inclusion criteria, this study was conducted in five high schools with 300 suitable students. The prevalence of smokers, age, age at smoking initiation, smoking duration, mean CO levels, and PEFR values among high school students in Banda Aceh City are shown in Table 1.

Table 1. Sample characteristics

Variable	Smoking status	
	Smoker (n=189)	Non-smoker (n=111)
Age (years)		
Mean±SD*	17.55±0.738	17.61±0.676
Median (min-max)**	18 (16–19)	18 (16–19)
Age at smoking initiation (years)		
Mean±SD*	13.5±0.926	---
Median (min-max)**	13 (12–16)	---
Smoking duration (years)		
Mean±SD*	4.04±1.166	---
Median (min-max)**	4 (1–7)	---
CO level (ppm)		
Mean±SD*	12.61±3.342	2.46±0.569
Median (min-max)	13 (5–21)	2 (2–4)
PEFR value (L/min)		
Mean±SD*	317.77±47.650)	408.10±35.381
Median (min-max)	300 (200–400)	400 (250–450)

In the group of students who smoke, 140 students (74.1%) have parents who smoke, and 118 students (62.4%) have non-parental families who smoke. In the nonsmokers' group, 92 (82.9%) students had parents who smoke, and 76 (68.5%) students had families other than their smoking parents. The normality test results using the Kolmogorov-Smirnov test showed that the CO levels and PEFR values were not normally distributed. The results of the Mann-Whitney test show a relationship between smoking with CO levels and PEFR scores in high school students in Banda Aceh City, as shown in Table 2.

Table 2. The relationship between smoking status and CO levels

Smoking status	CO Levels (ppm)		PEFR value (ppm)	
	Mean±SD	*P*	Mean±SD	*P*
Smoker	12.61±3.342	0.0001*	317.77±47.650	0.0001*
Non-smoker	2.46±0.569		408.10±35.381	

Note: *Mann-Whitney test

Based on the Spearman correlation, a relationship exists between smoking duration with CO levels and PEFR values, as shown in Table 3.

Table 3. The relationship between smoking duration with CO levels and PEFR values

Variable	Correlation coefficient	*P*
CO level	0.749	0.0001*
PEFR value	-0.554	0.0001*

Note: *Spearman correlation

DISCUSSION

The results of this study showed that the number of students in Banda Aceh City who smoke is higher than nonsmokers, which is 63%. This result is consistent with Baseline Health research in Indonesia year 2013 that as many as 64.9% of men over 15 years are smokers.[3] Research conducted by Sari in Padang showed that 59.1% of high school students in Padang were smokers.[9] Based on the 2013 Global Youth Tobacco Survey report, the proportion of smokers aged 15–19 years was 56.9%.[4] This age group is the age of high school students in Banda Aceh City.

Adolescence is the transition period from childhood to adulthood, characterized by physical, mental, and emotional changes. Adolescence is also a period where the environment and peers influence attitudes and behavior more.[10] One study showed a relationship between peer interaction and family interaction with smoking behavior in adolescents.[11]

The results of this study also indicated a relationship between smoking status and CO levels among high school students in Banda Aceh City. The CO levels of the student who smoke were 10.15 ppm higher than those of the nonsmokers. The result aligns with a study by Paskaria that showed higher CO levels in Purwakarta student smokers than in non-smoking students.[11] Another study of workers and visitors to the Persahabatan Hospital in Jakarta showed the same results, the CO levels in the smoker group were higher than the CO levels in the nonsmoker group.[12]

Aside from Indonesia, a study in Thailand of respondents aged 16–70 years showed that smokers had an mean expiratory CO level of 11.24 ppm. This value is significantly higher than for nonsmokers with an mean expiratory CO level of 2.25 ppm.[13] In study involving healthy respondents of Turkish smokers and nonsmokers, Deveci et al noted that CO levels were higher in smokers than nonsmokers (17.13 vs. 3.61). They even compared the CO levels of active smokers with those of passive smokers. As a result, CO levels are higher in active smokers than in passive smokers.[14] The finding of Hrabovsky et al also showed that smokers had higher expiratory CO levels than nonsmokers.[15]

Carbon monoxide is the main constituent of

cigarette smoke.[16] Carbon monoxide gas inhaled with cigarette smoke absorbs by the blood vessels and then binds to hemoglobin in the blood, forming carboxyhemoglobin (COHb), which will bind oxygen more efficiently than hemoglobin.[17] Smokers can have COHb levels as high as 5.6%, while smokers with lung disease have COHb levels above 10%.[18] COHb levels in the blood correlate well with expiratory CO levels and have a very high sensitivity. Therefore, the results of measuring the CO levels in this study also correlate very well with smoking status in students.[18]

The PEFR value in this study also has a significant relationship with smoking status. For smoking students, the mean PEFR value is lower than the mean PEFR value for nonsmokers, with a difference of 90.33 L/minute. In their study involving intermediate students in Bandar Lampung, Soemarwoto et al noted that student smokers (both active and passive) had lower PEFR scores than nonsmokers.[19] According to a Faqilah study in Bogor, adolescent smokers aged 15–19 years had higher PEFR values than nonsmokers in the same age range (470.22 L/min vs. 500.87 L/min). This is due to inflammation, fibrosis, goblet cell metaplasia, and smooth muscle hypertrophy in the airways of smokers, resulting in the narrowing of the airways.[20]

Age and smoking habits are several aspects that influence the PEFR value. From childhood to adolescence, 22–24 years of age, there is a development of pulmonary function, which an increase in the value of PEFR can assess. The PEFR value describes the function of the airways and lung tissue. Smoking can affect the function of the respiratory tract and lung tissue, affecting the PEFR value. The study included the age of student smokers into adolescence, with an mean smoking duration of 4 years, so the damage to the respiratory tract was not too severe. [21]

The mean PEFR value of non-smoking students in this study was 408.10 L/min, which was lower than the results of previous studies in the nonsmoker group.[19] This may be due to exposure to tobacco smoke from the environment, especially the environmental families. The study found that 82.9% and 68.5% of parents and families smoked in groups of nonsmokers, respectively.[21]

CO levels and PEFR values in this study were also strongly correlated with smoking duration (r=0.749 for CO levels, r= -0.554 for PEFR values). The more extended period of smoking is consistent with the higher CO level and the lower PEFR value. This is consistent with studies by Hilyah et al and Sukreni et al, who also mentions a strong relationship between smoking duration and CO and PEFR levels.[22,23] The longer a person smokes, the more frequently he will be exposed to CO gas from cigarette smoke, and therefore more CO gas will bind to hemoglobin than oxygen. This can be detected by measuring CO levels in the exhaled air.[24] The effects of smoking will be seen if the smoking duration was longer than two years, i.e., the PEFR values decreased due to airway changes caused by inflammatory processes.[25]

LIMITATION

Several limitations of this study were the cross-sectional design, where it could only be observed and measured at one time, so the course of smoking on increasing CO levels and decreasing PEFR values could not be seen. In addition, PEFR measurements were performed in a sitting position, not a standing one. Another limitation is that this study did not consider factors that cause high CO levels or low PEFR values in the student group of smokers since living environment factors can also influence CO levels and PEFR values.

CONCLUSION

From this study, it can be concluded that there is a relationship between smoking, CO levels, and PEFR values. High levels of CO and low PEFR values in the student who is a smokers are influenced by the length of time they smoke. Environmental factors can influence CO levels and PEFR of both smoker and nonsmoker students, that is, exposure to CO gas from smoking parents or families. Therefore, it is necessary to advise students, parents, and immediate family about the dangers of smoking.

Another thing that needs to be done is further research is needed to identify other factors that affect smoking behavior, CO levels, and PEFR levels in Banda Aceh students.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. Gray KM, Baker NL, Mcclure EA, Tomko RL, Squeglia LM, Saladin ME, et al. Efficacy and safety of varenicline for adolescent smoking cessation: A randomized clinical trial. JAMA Pediatr. 2019;173(12):1146–53.
2. World Health Organization. WHO global report on trends in prevalence of tobacco use 2000-2025. 3rd ed. 2019.
3. Kementerian Kesehatan RI. Riset Kesehatan Dasar 2013. Jakarta: Kementerian Kesehatan RI; 2013.
4. World Health Organization. Regional Office for South-East Asia. Global Youth Tobacco Survey (GYTS) Indonesia Report, 2014 [Internet]. New Delhi: WHO Regional Office for South-East Asia; 2015. Available from: https://apps.who.int/iris/handle/10665/205148
5. World Health Organization. Global Youth Tobacco Survey (GYTS) Fact Sheet Indonesia 2019. 2019.
6. Vasthare R, Kumar S, Arron L. Carbon monoxide breath analyzers and its role in tobacco cessation: A narrative review of literature. Journal of International Oral Health. 2018;10(2):71–6.
7. World Health Organization. Health effects of smoking among young people [Internet]. World Health Organization; 2013 [cited 2021 Jan 15]. Available from: https://www.who.int/tobacco/control/populations/yo uth_health_effects/en/
8. Nawafleh HA, Al-Sayed Abo Zead S, Al-Maghaireh F. Pulmonary function test: The value among smokers and nonsmokers. Health Science Journal. 2012;6(4):703–13.
9. Sari A, Kesehatan P, Padang K, Korespondensi A. Perilaku merokok di kalangan siswa Sekolah Menengah Atas di Kota Padang. Jurnal Ilmiah Kesehatan Masyarakat: Media Komunikasi Komunitas Kesehatan Masyarakat. 2019;11(3):238–44.
10. Rachmat M, Thaha RM, Syafar M. Perilaku merokok remaja Sekolah Menengah Pertama. Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal). 2013;7(11):502–8.
11. Paskaria C, Fransisca F, Kurnia J, Gunawan Z, Gunawan D. Students' smoking profile at Sukatani Village, Purwakarta. Jurnal Respirologi Indonesia. 2018;38(4):199–202.
12. Inayatillah IR, Syahrudin E, Susanto AD. Kadar karbon monoksida udara ekspirasi pada perokok dan bukan perokok serta faktor-faktor yang mempengaruhi. Jurnal Respirologi Indonesia. 2014;34(4):180–90.
13. Chatrchaiwiwatana S, Ratanasiri A. Exhaled carbon monoxide levels among tobacco smokers by age. Southeast Asian J Trop Med Public Health. 2017;48(2):429–37.
14. Deveci SE, Deveci F, Açik Y, Ozan AT. The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. Respir Med. 2004;98(6):551–6.
15. Hrabovsky S, Yingst JM, Veldheer S, Hammett E, Foulds J. Measurement of exhaled breath carbon monoxide in clinical practice: A study of levels in Central Pennsylvania community members. J Am Assoc Nurse Pract. 2017;29(6):310–5.
16. Herawati MH. Bahan yang mengandung zat adiktif pada produk rokok dan dampaknya terhadap kesehatan. In: Temu Ilmiah jaringan kerjasama kimia Indonesia. Yogyakarta; 2010.

17. Hall JE. Guyton and hall textbook of medical physiology. 12th ed. Elsevier - Health Sciences Division; 2010.
18. Hampson NB, Piantadosi CA, Thom SR, Weaver LK. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. Am J Respir Crit Care Med. 2012;186(11):1095–101.
19. Soemarwoto RA, Mustofa S, Rusmini H, Sinaga F, Fadhila N. The effects of active and passive smoking to predicted peak expiratory flow rate and oxygen saturation among Indonesian primary school children (aged 10–13 years) in Bandar Lampung, Indonesia. Chest. 2019 Oct 1;156(4):A1100.
20. Faqilah A. Perbedaan nilai arus puncak ekspirasi antara perokok dengan intensitas ringan dan bukan perokok pada siswa SMA usia 15-18 tahun di Kecamatan Cibinong Kabupaten Bogor Jawa Barat periode 2018. [Jakarta]: Universitas Pembangunan Nasional "Veteran" Jakarta; 2018.
21. Medabala T, Rao BN, Glad Mohesh MI, Praveen Kumar M. Effect of cigarette and cigar smoking on peak expiratory flow rate. J Clin Diagn Res. 2013;7(9):1886–9.
22. Hilyah RA, Lestari F, Mulqie L. Hubungan antara kebiasaan merokok dengan kadar karbon monoksida (CO) perokok. Jurnal Ilmiah Farmasi Farmasyiah. 2021;4(1):1–5.
23. Sukreni NPS, Wibawa A, Dinata IMK. Hubungan jumlah konsumsi batang rokok terhadap nilai arus puncak ekspirasi pada laki-laki dewasa muda. Majalah Ilmiah Fisioterapi Indonesia. 2017;5(3):49–52.
24. Martin T. The effects of carbon monoxide from cigarette smoking [Internet]. verywellmind. 2020 [cited 2020 Dec 13]. Available from: https://www.verywellmind.com/carbon-monoxide-in-cigarette-smoke-2824730
25. Abdulrahman WF. Effect of smoking on peak expiratory flow rat in Tikrit University. Tikrit Medical Journal. 2011;17(1):11–8.

Original Article

The Effect of Dexamethasone on IL-6 Levels in Confirmed COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

Bobby Hasibuan, Irvan Medison, Fenty Anggrainy

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Dr. M Djamil General Hospital Padang, West Sumatera, Indonesia

Abstract

Background: Elevated IL-6 levels have been found in COVID-19 patients and are associated with a poor prognosis. According to COVID-19 management guidelines, several types of corticosteroids can be used as therapy modalities for COVID-19 patients, including dexamethasone, methylprednisolone, and hydrocortisone. The purpose of this study was to examine how dexamethasone administration affected changes in IL-6 levelsin confirmed COVID-19 patients at RSUP Dr. M. Djamil Padang.

Methods: This was a retrospective cohort study with a sample of all COVID-19 patients who met the inclusion and exclusion criteria and were treated in the COVID-19 isolation ward at Dr. M. Djamil General Hospital

Padang. The study began in June 2021 and concluded in July 2022. The data were analyzed both descriptively and analytically. The distribution of frequencies and proportions of each variable was included in the univariate analysis. The bivariate analysis employs data-scale-appropriate statistical tests such as the T-test to determine the relationship between independent and dependent variables.

Results: The characteristic of the patients were mostly 18-49 years old (37.22%), female (55.67%), of severe clinical degree (49.44%), had no comorbidities (52.78%) and the majority (77.78%) received dexamethasone in the recommended dose (1 x 6 mg). The study's findingsrevealed that there was no difference in IL-6 values before and after dexamethasone administration in patients with moderate clinical degrees, but there were differences in IL-6 values before and after dexamethasone administration in patients with severe and critical clinical degrees.

Conclusion: The IL-6 level has significantly decreased following dexamethasone administration. Dexamethasone administration causes significant changes in IL-6 values in severe and critical degrees but not in moderate clinical degrees.

Keywords: COVID-19, dexamethasone, IL-6

Corresponding Author:
Bobby Hasibuan | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Dr. M. Djamil General Hospital Padang, West Sumatera, Indonesia | hasibuan86@yahoo.com

Submitted: November 29th, 2022
Accepted: July 23rd, 2023
Published: July 30th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 210–20
https://doi.org/10.36497/jri.v43i3.426

INTRODUCTION

The COVID-19 infection can be mild, moderate, severe, or critical. The most common clinical symptoms are fever (temperatures above 38 °C), cough, and difficulty in breathing. Other symptoms include severe shortness of breath, fatigue, myalgia, gastrointestinal symptoms like diarrhea, and other respiratory symptoms. Severe clinical deterioration occurs rapidly and gradually, such as in ARDS, septic shock, difficult-to-correct metabolic acidosis, and bleeding or coagulation system dysfunction within a few days.[1]

A viral infection causes an immune response against the virus, which can cause lung tissue damage, functional impairment, and decreased lung capacity if the immune response is uncontrollable. Macrophages initiate the immune response by presenting the SARS-CoV-2 antigen to T cells, which activate and release cytokines and chemokines such as interleukin (IL)-1, IL-6, IL-8, IL-21, tumor necrosis factor (TNF), and monocyte chemotactic protein (MCP)-1. Cytokine storms that stimulate lymphocytes and leukocytes to migrate to the site of infection can be caused by certain conditions.[2]

As the disease progresses, large amounts of cytokines are secreted, one of which is interleukin 6 (IL-6).[3] Interleukin 6 is a pleiotropic biomolecule that is secreted by many different cell types involved in inflammation, immune response, and hematopoiesis. Wan et al discovered elevated IL-6 levels in one-third of patients with mild symptoms and three-quarters of patients with severe symptoms in their study. Diao et al discovered an inversely proportional relationship between increased IL-6 levels and T-cell counts in

ICU patients. This discovery is based on the theory that SARS-CoV-2-induced cytokines can impair T cells' ability to eliminate pathogens.[4] High systemic IL-6 levels are associated with clinically severe COVID-19, which is mostly associated with respiratory distress syndrome.[5] Elevated IL-6 levels have been found in COVID-19 patients and are associated with a poor prognosis.

Corticosteroids are one of the therapeutic modalities that have a physiological role in inflammation and the immune system, as well as an effect on different cytokines.[6,7] Corticosteroids reduce the number and activation of inflammatory cells, including mast cells, macrophages, T lymphocytes, and eosinophils, as well as inflamed tissues, in all chronic inflammatory and immune diseases.[8] According to COVID-19 management guidelines, several types of corticosteroids can be used as therapeutic modalities for COVID-19 patients, including dexamethasone, methylprednisolone, and hydrocortisone.[9]

Awasthi et al discovered that after corticosteroid administration, 7 out of 10 patients had stable or decreased IL-6 levels.[10] Andre et al investigated the role of IL-6 as a biomarker of fatal SARS-CoV-2 pneumonia;IL-6 levels were measured when the patient was admitted, every 72 hours during hospitalization, and when the patient was discharged. This study discovered that the peak of IL-6 was time-limited and that IL-6 levels returned to normal after the 10th day.[11]

Another study from Julie et al took the first average measurement of IL-6 levels 4 (2-7) days after the patient was admitted, the second after 6 (6-11) days, and the third after 11 (10-15) days.[1212] This study found a significant difference in IL-6 levels in patients with a higher risk of death (720 pg/ml) versus those with a better prognosis (336 pg/ml).

METHODS

This research was a retrospective cohort study. From June 2021 to July 2022, this study was carried out in the COVID-19 isolation ward at RSUP Dr. M. Djamil Padang. All COVID-19 patients treated in the COVID-19 isolation ward at RSUP Dr. M. Djamil Padang who met the inclusion and exclusion criteria were included in the study. All confirmed COVID-19 patients aged >18 years who received dexamethasone therapy with IL-6 values >7, had complete medical record data in the form of pre- and post-IL-6 laboratory tests (6-11 days) and dexamethasone administration and had a diagnosis of clinical doctor in charge of service were eligible for the study. COVID-19 patients who had received dexamethasone therapy before being admitted to RSUP Dr. M. Djamil, as well as COVID-19 patients receiving IL-6 therapy, were excluded from the study.

RESULTS

The inclusion and exclusion criteria were met by 180 samples. Table 1 shows the characteristics of confirmed COVID-19 patients at RSUP Dr. M. Djamil Padang.

Table 1. The characteristics of COVID-19 patients (N=180)

Characteristic	n	%
Age		
18-49 years	67	37.22
50–59 years	44	24.44
60–69 years	42	23.33
≥70 years	27	15.00
Gender		
Male	80	44.44
Female	100	55.56
Clinical severity of COVID-19		
Mild	25	13.89
Severe	89	49.44
Critical	66	36.67
Comorbid		
No comorbid	95	52.78
1 comorbid	56	31.11
>1 comorbids	29	16.11
Corticosteroid dose		
According to the guideline	140	77.78
Above the guideline	40	22.22

The majority of study participants (37.22%) were between the ages of 18 and 49 and were female (55.56%). The most common degree was severe clinical degree (49.44%), followed by critical degree (36.67%). The majority of subjects had no comorbidities (52.78%). The majority of patients (77.78%) received dexamethasone at the recommended dose (1 x 6 mg).

Table 2. The relationship between dexamethasone administration and changes in IL-6 values in COVID-19 patients based on clinical degrees.

Dexamethasone Administration	IL-6 Level (pg/mL)			*P*
	Min-Max	Median (Q1-Q3)	Mean±SD	
Before	8.1–2342.00	77.00 (26.43– 182.88)	156.91±244.68	0.0001*
After	1.5–732.5	45.25 (15.45 – 120.60)	83.84±45.25	

Note: *Wilcoxon rank test

Table 3. The relationship between dexamethasone administration and changes in IL-6 values in COVID-19 patients based on clinical degrees.

Severity Degree	IL-6 Level (pg/mL) [Median Min–Max)]		*P*
	Before Dexamethasone Administration	After Dexamethasone Administration	
Mild (n=25)	54.70 (9.20–528.00)	20.20 (1.50–271.00)	0.137
Severe (n=89)	77.20 (8.10–999.00)	31.50 (1.50–491.50)	0.0001
Critical (n=66)	81.65 (8.20–2342.00)	70.35 (0.50–732.50)	0.0001

Note: *Wilcoxon rank test

According to Table 2, the IL-6 level before dexamethasone administration ranged from 8.1 to 2,342 pg/mL. After dexamethasone administration, IL-6 levels ranged from 1.5 to 732.5 pg/mL. Because the normality requirement for data distribution for changes in IL-6 values was not met, the correlation between dexamethasone administration and changes in IL-6 values was analyzed using a non-parametric unpaired 2-group difference test, namely the Wilcoxon signed ranks test (from the Kolmogorov-Smirnov test results with *P*=0.0001 was obtained). The Wilcoxon signed ranks test yielded *P*=0.0001, indicating that there was a significant difference in IL-6 values before and after dexamethasone administration, indicating the existence of a relationship between dexamethasone administration and changes in IL-6 values.

Table 3 depicts the relationship between dexamethasone administration and changes in IL-6 values based on the clinical severity of the disease. For moderate clinical degrees, the Wilcoxon signed ranks test yielded *P*=0.137 and *P*=0.0001 for severe and critical clinical degrees, respectively. Dexamethasone administration did not affect IL-6 values at moderate clinical levels, but it did have an effect on IL-6 values at severe and critical levels.

Table 4 demonstrates a link between clinical comorbidities and changes in IL-6 levels in confirmed COVID-19 patients. The Kruskal-Wallis test yielded *P*=0.030 for a comparison of changes in IL-6 values in moderately severe and critically ill COVID-19 patients.

Based on the average value of changes in IL-6 levels, it can be seen that patients with comorbidities >1 have the smallest rate of decline (8.20 pg/mL), followed by patients with 1 comorbidity and those without comorbidities, who have higher rates, namely 10.20 and 40.90 pg/mL. COVID-19 patients with more than one comorbidity had lower changes (decreases) in IL-6 values than COVID-19 patients with only one comorbidity or no comorbidity.

Table 4. The relationship between dexamethasone administration and changes in IL-6 levels in COVID-19 patients based on comorbidities.

Comorbid	Changes in IL-6 Level (pg/mL) [Median (Min-Max)]	*P*
No comorbid	40.90 (-100.70 – 799.10)	0.030*
1 comorbid	10,20 (-101.00 – 2237.20)	
>1 comorbids	8,20 (-100.10 – 482.10)	

Note: *Kruskal-Wallis test

Table 5 demonstrates that there is no relationship between dexamethasone dose and changes in IL-6 levels in confirmed COVID-19 patients. This is demonstrated by the acquisition of *P*=0.715 from the Mann-Whitney test for a comparison of changes in IL-6 values in COVID-19 patients at the recommended dose of dexamethasone and the dose above the guideline. Based on the mean value of changes in IL-6 levels, it can be seen that the rates of decline in IL-6 values in patients who received dexamethasone at the recommended dose and above the recommended dose were relatively similar, namely 21.92 and 21.90 pg/mL.

Table 5. Relationship between the dose of dexamethasone and changes in IL-6 values in COVID-19 patients

Dose of Dexamethasone	Changes in IL-6 Level (pg/mL) [Median (Min-Max)]	*P*
According to the guideline	21.92 (-100.10 – 799.10)	0.715
Above the guideline	21.90 (-101.00 – 2,237.20)	

Note: *Mann-Whitney test

DISCUSSION

The patients in this study were mostly between the ages of 18 and 49 (37.2%), with only a small proportion over the age of 70 (15.0%). The findings of this study are consistent with the study conducted in 2020 by Mudhaffer in Iraq, which discovered that the majority of COVID-19 patients were between the ages of 20 and 50.[13] The high prevalence of COVID-19among patients aged 18-49 years can be attributed to the fact that this age group is in the working-age category with the highest mobility and is followed by more interpersonal interactions. According to a study conducted in 2022 by Tabernero et al in Spain, the number of COVID-19 cases among young adults worldwide was increasing rapidly. Wider use of diagnostic tests has identified individuals in this population group as accounting for 75% of COVID-19 cases.[14]

This study's findings are inversely proportional to the findings of a 2020 study conducted by Belda in Spain, which obtained the highest prevalence of COVID-19 patients aged 70 years (44.6%) and only 15.3% of patients aged 18-49 years.[15] The elderly are at a higher risk of developing COVID-19, which can be accompanied by progressive clinical deterioration. Inflammaging is associated with immunosenescence, which is characterized by disturbances in the innate and adaptive immune systems as well as the continuous production of inflammatory mediators and cytokines. In older people, abnormal ciliary function and ciliary ultrastructure can also interfere with the successful cleaning of SARS-CoV-2 virus particles; this puts patients at a higher risk of contracting COVID-19.[16]

Older people, immunosenescence, and co-morbidities are more likely to set off a viral-induced cytokine storm, which can lead to life-threatening respiratory failure and multisystemic involvement.[16] The age of the patient is a risk factor for disease severity and mortality. According to a 2020 study from Liu et al in China, COVID-19 patients over 60 had a higher rate of respiratory failure and required more hospitalization than patients under 60.[17] According to other sources, the mortality rate rises with age. The risk of death was 3% in patients over the age of 50, 16% in those aged 50-59, 22% in those aged 60-69, and 34% in those over 70.[18]

More than half of the patients (55.6%) in this study were female. These findings are similar to those of Fortunato in Foggia in 2020, who discovered that 50.7% of COVID-19 patients were female.[19] There is evidence that men and women are equally at risk of SARS-CoV-2 infection, but men are at a higher risk of death when compared to women.[20]

A study from Doerre in 2021 in Germany using contact matrices discovered a pattern in which women had a higher presentation of contact with COVID-19 (13-26%) at the age of 20-39 years, but as age increases, especially in the range 50-69 years, men had a 9-14% higher contact presentation. Due to a greater number of contacts, young and middle-aged women contribute to an increase in the incidence of infection. Sex differences in contact rates may be one of the pathways that contribute to disease spread and lead to sex-specific infection rates and mortality outcomes.[21]

This study is inversely proportional to the findings of a 2020 study conducted by Raimondi in Italy, which discovered that the majority of COVID-19 patients (72.4%) were male.[22] The mechanism underlying the gender bias in COVID-19 is unknown, but it is thought to be linked to angiotensin-converting enzyme 2 (ACE2) expression, which is an important enzyme of the renin-angiotensin system (RAS) and a functional receptor for SARS-CoV and SARS-CoV2 infection. It has been demonstrated that ACE2 protects against chronic diseases such as hypertension, cardiovascular disease, and acute respiratory distress syndrome (COVID-19).[23]

According to research, SARS-CoV infection causes ACE2 down-regulation by binding the viral spike protein to ACE2, reducing ACE2 expression in the lungs, and causing acute respiratory failure. Because COVID-19 and SARS patients have similar acute respiratory distress syndromes and gender biases in disease susceptibility and mortality rates, this pathogenic mechanism is also present in COVID-19 cases.[23]

Different lifestyles between sexes, such as behaviors more commonly found in males than females, are also thought to be potential risk factors for COVID-19 occurrence. In general, women have more intense and stronger innate and adaptive immune systems than men, which aids in viral clearance. Estrogen, the primary female sex hormone, has been shown to protect against SARS by not only activating the immune response but also directly suppressing SARS-CoV replication. Estrogen is also known to inhibit the activity or expression of various renin-angiotensin system components, and it has been shown to specifically increase ACE2 expression.[23]

According to the clinical degree of COVID-19, the majority of respondents (49.4%) were in the severe category, followed by the critical category (36.7%) and the moderate category (13.9%). This study's findings are consistent with a study conducted by Li et al in Wuhan, China, which found that 49.1% of patients were in a severe category. This was because Wuhan experienced the highest peak of the COVID-19 outbreak, with family clusters and a high prevalence of COVID-19 in older adults, from mid-January to early February.[24]

The findings of this study are not similar to a 2020 research by Liu in Beijing on the use of corticosteroids in different clinical categories of COVID-19. According to this study, the majority of the patients (49.53%) were in the moderate category, followed by the critical (23.88%), and severe category (12.31%).[25] In 2020, Gong conducted a study in Shanghai on the severity of COVID-19 with inflammatory parameters and discovered that 34% of patients were in the severe category and 32% were in the critical category.[26]

According to this study, about 52.8% of subjects had no comorbidities. These findings are similar to a study by Surendra, which pointed out that 69% of patients with confirmed COVID-19 had no comorbidities. Only 31% of the patients in that study had one or more comorbidities, such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD), or chronic kidney disease.[18] Endothelial dysfunction is promoted by inflammatory cardiovascular risk factors such as dyslipidemia, obesity, and diabetes. Mast cells, T lymphocytes, dendritic cells, activated neutrophils, and platelets collaborate to produce an inflammatory response that includes increased production of pro-inflammatory cytokines, reactive oxygen species (ROS), and adhesion molecules.[27]

Bordallo et al discovered that 57% of patients with severe COVID-19 had hypertension, 42% were obese, and 34% had diabetes in a 2020 study in Brazil. The metabolic syndrome and obesity, according to the literature, develop as a result of chronic inflammation caused by increased NF-B activity and the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. Patients with hypertension also have endothelial cell dysfunction and immunometabolic changes, which contribute to higher inflammatory cytokine levels in the blood.[28] In general, the mortality rate is 3% in patients without comorbidities, 8% in patients with one comorbidity, and27% in patients with more than one comorbidity.[18]

Dexamethasone was administered to all patients as corticosteroid therapy. About 77.8% of patients received corticosteroid doses following the guidelines. According to the COVID-19 management guidelines, corticosteroids can be considered for initialuse in moderate, severe, and critical COVID-19 patients.[9] The dose of dexamethasone corresponds to the COVID-19 management guidelines, namely 0.15 mg/kg BW per day given every 24 hours with a maximum dose of 6 mg.[9,29] Dexamethasone is strongly recommended by the Infectious Diseases Society of America (IDSA) for critically ill patients with acute respiratory distress syndrome (ARDS) and systemic inflammation. Dexamethasone at a total daily dose of 6 mg IV or PO for 10 days (or until discharge) is recommended, as are other glucocorticoids such as methylprednisolone (32 mg) and prednisone (40 mg). As the severity of the disease decreases, so does the recommendation rate. Glucocorticoids are not recommended in non-severe COVID-19 patients due to a lack of strong evidence.[29]

Granholm et al concluded that there was no statistically significant difference in mortality or

health-related quality of life (HRQoL) between the use of dexamethasone 12 mg and 6 mg in patients with COVID-19 and severe hypoxemia, but the benefits of high-dose dexamethasone were more compatible.[30] Fakhriravari et al found a reduction in 28-day all-cause mortality in 2104 patients who received low-dose dexamethasone (6 mg) orally or IV once daily for 10 days compared to patients who received usual care.[31]

Elevated IL-6 levels have previously been observed in patients with respiratory dysfunction, implying that COVID-19 may cause cytokine-mediatedlung damage. SARS-CoV-2 infection is also extremely pathogenic, with rapid viral replication and a proclivity to infect the lower respiratory tract, which increases the severity of IL-6-induced severe respiratory distress. Serial measurement of circulating IL-6 levels may be useful in identifying disease progression in COVID-19-infected patients.[32] According to Table 2, the IL-6 value before corticosteroid administration ranged from 8.1 to 2,342 pg/mL, with a mean of 156.91 pg/mL and a median of 77.00 pg/mL. Ananda et al discovered that 83.9% of patients had IL-6 levels of 100 pg/mL, with only a small number of patients (16.1%) having normal IL-6 levels. According to their study, the lowest IL-6 level was 2.7 pg/mL, while the highest level was 244 pg/mL.[33]

Interleukin-6 is found in healthy people's blood at very low levels, around 1-5 pg/mL. In inflammatory conditions, IL-6 concentrations rise gradually and can reach the g/mL range in cases of sepsis.[34] Han et al investigated the predictive value of various cytokines and obtained that IL-6 was the best predictor of severe COVID-19.[35] A meta-analysis of nine studies concluded that elevated IL-6 levels were strongly related to disease severity. According to this study, patients with severe COVID-19 had an average IL-6 value of 58 pg/mL. This was a very high value when compared to the IL-6 level in patients with mild disease, which was only 17 pg/mL.[36] According to Herold et al, IL-6 levels greater than 80 pg/mL can predict the likelihood of respiratory failure and the need for mechanical ventilation in COVID-19 patients.[37] Chen et al discovered a cutoff of 80 pg/mL to distinguish between living and dead patients.[38]

The inflammatory process in COVID-19 begins with the novel coronavirus binding to the ACE2 receptor, which is expressed by alveolar epithelial cells, allowing the virus to enter the cell endosomally. Infected cells can undergo apoptosis or necrosis after virus replication, assembly, and release, triggering an inflammatory response by producing proinflammatory cytokines. TLRs, which aid innate immunity in recognizing infectious pathogens, can also activate macrophages and monocytes, causing them to release IL-6.[32,36]

After corticosteroid administration, IL-6 levels ranged from 1.5 to 732.5 pg/mL, with a mean of 83.84 pg/mL and a median of 45.25 pg/mL. Corticosteroids are anti-inflammatory medications that have long been known to inhibit pro-inflammatory cytokines like IL-2, IL-3, IL-4, IL-5, and IL-6.[39] Awasthi discovered IL-6 values more than twice the upper limit of normal (normal reference range 0.31-5 pg/mL) before corticosteroid administration in a study on IL-6 values after corticosteroid administration. After corticosteroid administration, five of ten patients had mean IL-6 levelsless than twice the upper limit of normal (10 pg/mL), and four of ten patients had IL-6 levels less than 5 pg/mL.[10]

A retrospective study of 90 confirmed severe and critical COVID-19 cases in Wuhan following treatment with various types of corticosteroids revealed a significant improvement in clinical parameters and chest CT images in patients receiving corticosteroids. This study provided experimental and clinical evidence that corticosteroids at medium to low doses could protectthe respiratory and digestive systems by activating ACE2 and suppressing cytokine storms.[39]

The Wilcoxon signed ranks relationship between dexamethasone administration and changes in IL-6 values obtained a P=0.0001, indicating that there was a significant difference in IL-6 values before and after dexamethasone administration, implying that there is a relationship between dexamethasone administration and changes in IL-6 values. These findings are consistent with those of Valle et al, who stated that patients treated with corticosteroids and remdesivir had a

rapid and gradual decrease in IL-6 levels when compared to patients who did not receive this treatment. This study observed that among several types of corticosteroids, dexamethasone had the greatest IL-6-lowering effect. Namazi stated in his research conducted in Saudi Arabia in 2022 that glucocorticoids could reduce SARS-CoV-2 infection by lowering IL-6 levels. Dexamethasone is reported to be the drug of first choice for the treatment of respiratory disorders among all glucocorticoids.[40]

The findings of this study are inversely proportional to those of Awasthi, who found a weak correlation between changes in the average plasma IL-6 value after corticosteroid administration and outcomes 10 years later.[10] Similarly, a retrospective analysis of outcomes in COVID-19 patients who received and did not receive corticosteroid therapy revealed that inflammatory markers (e.g., CRP, PCT, white blood cells (WBC), D-dimer, IL-6, and IL-10) and some serum biochemical indicators did not differ significantly between the two groups.[41]

According to Fujino's research, dexamethasone therapy alone did not affect IL-6 levels. An analysis of transcriptomic data supports this, demonstrating that the mechanism of dexamethasone therapy in patients with severe COVID-19 does not involve the IL-6 pathway. The odds ratio (OR) of IL-6 was high when adjusted for previous dexamethasone administration, implying that IL-6 levels might reflect ongoing respiratory system damage even when the patient was receiving dexamethasone therapy.[42]

The mechanism of corticosteroid potential effect on IL-6 levels is linked to the expression profile of the NR3C1 gene, which is the highest affinity target for dexamethasone, methylprednisolone, and prednisone. T cells, B cells, monocytes, natural killer cells, dendritic cells, and macrophages were the immune cells with the highest NR3C1 expression. NR3C1 expression is particularly high in alveolar macrophages. In patients with confirmed COVID-19, both macrophages and T cells expressed high levels of NR3C1, whereas plasma, neutrophils, and epithelial cells in recovered patients expressed lower levels of NR3C1. If there is a bond between glucocorticoids and the glucocorticoid receptor of GR/NR3C1), it can suppress transcription of inflammatory genes directly through protein synthesis-independent processes (transrepression) or transcriptional activation (transactivation) of several anti-inflammatory/repression factors, thereby reducing IL-6 production locally and systemically, restoring immune homeostasis and reducing the development of acute respiratory failure.[10,43]

This study found no link between dexamethasone administration and changes in IL-6 values at moderate clinical levels, but there was a link between dexamethasone administration and changes in IL-6 values at severe and critical levels. Eric et al found that serum IL-6 levels were significantly higher inpatients with severe COVID-19 in a systematic review and meta-analysis. According to a meta-analysis of available data, elevated levels are significantly associated with adverse clinical outcomes such as ICU admission, ARDS, and death. Serum IL-6 levels in patients with clinically severe COVID-19 are nearly three times higher than in those without complications.[44]

Wang et al pointed out that patients with clinically severe COVID-19 were more likely to require additional corticosteroid therapy.[45] Patients with severe COVID-19 who have high IL-6 levels are more likely to benefit from cytokine blockade. A study conducted by Valle et al observed that dexamethasone had the highest IL-6 lowering effect among several types of corticosteroids, which was thought to underpin the effectiveness of treatment in these patients.[40]

A study by Chen et al on the relationship between the clinical phenotype of COVID-19 and response to corticosteroid therapy found that corticosteroid therapy was associated with lower 28-day mortality in patients with a hyperinflammatory phenotype (i.e., a condition characterized by increased levels of proinflammatory cytokines and SOFA score) but had no effect on patients with a hypoinflammatory phenotype.[46]

In confirmed COVID-19 patients, researchers obtained a correlation between clinical comorbidities and changes in IL-6 levels. COVID-19 patients with

>1comorbidity had lower changes (decreases) in IL-6 values than COVID-19 patients without comorbidities or with 1 comorbidity. COVID-19 patients with comorbidities have a rapid and severe disease course, which often results in death. According to Sanyaolu et al, the most common comorbidities among COVID-19 patients are hypertension (15.8%), cardiovascular and cerebrovascular disease (11.7%), and diabetes (9.4%). Meanwhile, the most common comorbidities were HIV and hepatitis B (1.5%), cancer (1.5%), respiratory disorders (1.4%), kidney disorders (0.8%), and immune deficiencies (0.01%).[47]

The response of patients to corticosteroid therapy varies. Many factors influence the effectiveness of corticosteroid therapy, including disease severity, inflammatory conditions, and comorbidities.[46] Due to the low comorbidity assessment, drug interactions, and lack of knowledge regarding pathway crosstalk between COVID-19 and comorbidities required to understand the complexity of pathogenesis, the management of COVID-19 patients with comorbidities is becoming more complex.[48]

This study found no correlation between dexamethasone administration doses and changes in IL-6 levels in COVID-19 patients. This is demonstratedby a Mann-Whitney test with *P*=0.715 for a comparison of changes in IL-6 values among COVID-19 patients at the recommended dose of dexamethasone and a dose higher than the guideline. These findings are consistentwith the study by Zuniga et al of COVID-19 patients with IL-6 levels of at least 40 pg/mL.[49] There were no clinically significant differences between patients who received high-dose corticosteroids, namely dexamethasone equivalent to 125 mg methylprednisolone, and patients who received low-dose corticosteroids, according to this study.[49]

A study of 65 COVID-19 cases in Beijing stated that corticosteroids could inhibit IL-6 production,but there was no statistically significant difference in IL-6 levels between patients receiving low doses (2 mg/kg/day) and high doses (>2 mg/kg/day). In other words, low doses of corticosteroids (2 mg/kg/day) could inhibit IL-6 production just as well as higher doses.[25]

According to the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, patients with severe and critical COVID-19 should take 6 mg of dexamethasone daily for 10 days. In his study, Perner pointed out that higher doses of corticosteroids were beneficial for patients with a more severe course of the disease. According to several meta-analyses, the most commonly used daily dose was dexamethasone at a dose of 6-16 mg (a median dose of 12 mg).[50]

LIMITATION

This was a retrospective cohort study using medical records data with uneven distribution of data and only assessed changes in IL-6 values in the administration of one corticosteroid.

CONCLUSION

In general, the characteristics of clinically confirmed COVID-19 patients at RSUP Dr. M. Djamil Padang revealed that respondents were mostly female, aged 18-49 years, and nearly half of them had comorbidities. Following dexamethasone administration, the IL-6 level decreased significantly. The administration of dexamethasone was associated with significant changes in IL-6 values in severe and critical clinical degrees, but not in moderate clinical degrees. In patients with comorbidities, the effect of dexamethasone administration on changes in IL-6 values was significant, but there was no relationship between dexamethasone administration dose and changes in IL-6 values.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Ikatan Dokter Indonesia. COVID-19. Jakarta: Ikatan Dokter Indonesia; 2020.
2. Gallelli L, Zhang L, Wang T, Fu F. Severe acute lung injury related to COVID-19 infection: A review and the possible role for escin. J Clin Pharmacol. 2020;60(7):815–25.
3. Magro G. SARS-CoV-2 and COVID-19: Is interleukin-6 (IL-6) the "culprit lesion" of ARDS onset? What is there besides Tocilizumab? SGP130Fc. Cytokine X. 2020;2(2):100029.
4. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). medRxiv. 2020;2020.02.18.20024364.
5. Gubernatorova EO, Gorshkova EA, Polinova AI, Drutskaya MS. IL-6: relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev. 2020;53:13–24.
6. Ali MJ, Hanif M, Haider MA, Ahmed MU, Sundas FNU, Hirani A, et al. Treatment options for COVID-19: A review. Front Med (Lausanne). 2020;7:558346.
7. Caramori G, Mumby S, Girbino G, Chung KF, Adcock IM. Corticosteroids. Nijkamp and Parnham's Principles of Immunopharmacology. 2019;661–88.
8. Yasir M, Goyal A, Sonthalia S. Corticosteroid adverse effects. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
9. PDPI, PERKI, PAPDI, PERDATIN, IDAI. Pedoman tatalaksana COVID-19: Edisi 4. Indonesia: 4; 2022.
10. Awasthi S, Wagner T, Venkatakrishnan AJ, Puranik A, Hurchik M, Agarwal V, et al. Plasma IL-6 levels following corticosteroid therapy as an indicator of ICU length of stay in critically ill COVID-19 patients. Cell Death Discov. 2021;7(1):55.
11. Santa Cruz A, Mendes-Frias A, Oliveira AI, Dias L, Matos AR, Carvalho A, et al. Interleukin-6 is a biomarker for the development of fatal severe acute respiratory syndrome coronavirus 2 pneumonia. Front Immunol. 2021;12:613422.
12. Gorham J, Moreau A, Corazza F, Peluso L, Ponthieux F, Talamonti M, et al. Interleukine-6 in critically ill COVID-19 patients: A retrospective analysis. PLoS One. 2020;15(12):e0244628.
13. Al-Mudhaffer RH, Ahjel SW, Hassan SM, Mahmood AA, Hadi NR. Age distribution of clinical symptoms, isolation, co-morbidities and case fatality rate of COVID-19 cases in Najaf City, Iraq. Medical Archives. 2020;74(5):363–7.
14. Tabernero E, Ruiz LA, España PP, Méndez R, Serrano L, Santos B, et al. COVID-19 in young and middle-aged adults: predictors of poor outcome and clinical differences. Infection. 2022;50(1):179–89.
15. Gómez-Belda AB, Fernández-Garcés M, Mateo-Sanchis E, Madrazo M, Carmona M, Piles-Roger L, et al. COVID-19 in older adults: What are the differences with younger patients? Geriatr Gerontol Int. 2021;21(1):60–5.
16. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: Insights into pathogenesis and clinical decision-making. Aging Clin Exp Res. 2020;32(8):1599–608.
17. Liu Y, Mao B, Liang S, Yang JW, Lu HW, Chai YH, et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur Respir J. 2020;55(5):2001112.
18. Surendra H, Elyazar IR, Djaafara BA, Ekawati LL, Saraswati K, Adrian V, et al. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study. Lancet Reg Health West Pac. 2021;9:100108.
19. Fortunato F, Martinelli D, Lo Caputo S, Santantonio T, Dattoli V, Lopalco PL, et al. Sex and gender differences in COVID-19: an Italian local register-based study. BMJ Open. 2021;11(10):e051506.
20. Fernández-De-las-peñas C, Martín-Guerrero JD, Pellicer-Valero ÓJ, Navarro-Pardo E, Gómez-Mayordomo V, Cuadrado ML, et al. Female sex is a risk factor associated withlong-term post-

COVID related-symptoms but not with COVID-19 symptoms: The LONG-COVID-EXP-CM multicenter study. J Clin Med. 2022;11(2):413.
21. Doerre A, Doblhammer G. The influence of gender on COVID-19 infections and mortality in Germany: Insights from age- and gender-specific modeling of contact rates, infections, and deaths in the early phase of the pandemic. PLoS One. 2022;17(5):e0268119.
22. Raimondi F, Novelli L, Ghirardi A, Russo FM, Pellegrini D, Biza R, et al. Covid-19 and gender: Lower rate but same mortality of severe disease in women-an observational study. BMC Pulm Med. 2021;21(1):96.
23. Gagliardi MC, Tieri P, Ortona E, Ruggieri A. ACE2 expression and sex disparity in COVID-19. Cell Death Discov. 2020;6(1):37.
24. Kidron R, Robinson S. The importance of computerized tomography in psychiatry. Israel Journal of Psychiatry and Related Sciences. 1982;19(2):165–72.
25. Liu F, Ji C, Luo J, Wu W, Zhang J, Zhong Z, et al. Clinical characteristics and corticosteroids application of different clinical types in patients with corona virus disease 2019. Scientific Reports 2020 10:1. 2020;10(1):1–9.
26. Gong J, Dong H, Xia QS, Huang Z yi, Wang D kun, Zhao Y, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: A retrospective study. BMC Infect Dis. 2020;20(1):963.
27. Su JH, Luo MY, Liang N, Gong SX, Chen W, Huang WQ, et al. Interleukin-6: A novel target for cardio-cerebrovascular diseases. Front Pharmacol. 2021;12:745061.
28. Bordallo B, Bellas M, Cortez AF, Vieira M, Pinheiro M. Severe COVID-19: What have we learned with the immunopathogenesis? Adv Rheumatol. 2020;60(1):50.
29. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: A randomized clinical trial. JAMA. 2020;324(13):1298–306.
30. Granholm A, Kjær MBN, Munch MW, Myatra SN, Vijayaraghavan BKT, Cronhjort M, et al. Long-term outcomes of dexamethasone 12 mg versus 6 mg in patients with COVID-19 and severe hypoxaemia. Intensive Care Med. 2022;48(5):580–9.
31. FakhriRavari A, Jin S, Kachouei FH, Le D, Lopez M. Systemic corticosteroids for management of COVID-19: Saving lives or causing harm? Int J Immunopathol Pharmacol. 2021;35:20587384211063976.
32. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev. 2020;53:38–42.
33. Yudistira R, Ananda D, Kurniati N, Hudari H, Bahar E. Correlation of interleukin-6 levels with clinical features and chest x-ray imaging in coronavirus disease-19 (COVID-19) patients at Dr. Mohammad Hoesin General Hospital Palembang. Bioscientia Medicina : Journal of Biomedicine and Translational Research. 2022;6(5):1799–805.
34. Wolf J, Rose-John S, Garbers C. Interleukin-6 and its receptors: A highly regulated and dynamic system. Cytokine. 2014;70(1):11–20.
35. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect. 2020;9(1):1123–30.
36. Mojtabavi H, Saghazadeh A, Rezaei N. Interleukin-6 and severe COVID-19: A systematic review and meta-analysis. Eur Cytokine Netw. 2020;31(2):44–9.
37. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128-136.e4.
38. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased

patients with coronavirus disease 2019: Retrospective study. BMJ. 2020;368:m1091.
39. Xiang Z, Liu J, Shi D, Chen W, Li J, Yan R, et al. Glucocorticoids improve severe or critical COVID-19 by activating ACE2 and reducing IL-6 levels. Int J Biol Sci. 2020;16(13):2382–91.
40. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636–43.
41. Xiong B, Du H, Zhan Z, Zhang A, He LM, Qin YY, et al. Effectiveness of adjunctive corticosteroid therapy in patients with severe COVID-19: A retrospective cohort study. World J Clin Cases. 2021;9(15):3546–58.
42. Fujino M, Ishii M, Taniguchi T, Chiba H, Kimata M, Hitosugi M. The value of interleukin-6 among several inflammatory markers as a predictor of respiratory failure in COVID-19 patients. Diagnostics (Basel). 2021;11(8):1327.
43. King EM, Chivers JE, Rider CF, Minnich A, Giembycz MA, Newton R. Glucocorticoid repression of inflammatory gene expression shows differential responsiveness by transactivation- and transrepression-dependent mechanisms. PLoS One. 2013;8(1):e53936.
44. Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: A systematic review and meta-analysis. Rev Med Virol. 2020;30(6):1–9.
45. Wang J, Yang W, Chen P, Guo J, Liu R, Wen P, et al. The proportion and effect of corticosteroid therapy in patients with COVID-19 infection: A systematic review and meta-analysis. PLoS One. 2021;16(4):e0249481.
46. Chen H, Xie J, Su N, Wang J, Sun Q, Li S, et al. Corticosteroid therapy is associated with improved outcome in critically ill patients with COVID-19 with hyperinflammatory phenotype. Chest. 2021;159(5):1793–802.
47. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069–76.
48. Barh D, Aljabali AA, Tambuwala MM, Tiwari S, Serrano-Aroca Á, Alzahrani KJ, et al. Predicting COVID-19-comorbidity pathway crosstalk-based targets and drugs: Towards personalized COVID-19 management. Biomedicines. 2021;9(5):556.
49. Zúñiga MÁL, Moreno-Moral A, Ocaña-Granados A, Padilla-Moreno FA, Castillo-Fernández AM, Guillamón-Fernández D, et al. High-dose corticosteroid pulse therapy increases the survival rate in COVID-19 patients at risk of hyper-inflammatory response. PLoS One. 2021;16(1):e0243964.
50. The COVID STEROID 2 Trial Group. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: The COVID STEROID 2 randomized trial. JAMA. 2021;326(18):1807–17.

Case Report

Case Report: Pneumonia Like Mass with Spontaneous Resolution

Aisyah Ayu Safitri, Muhammad Fahmi Alatas

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Regional Hospital, Jakarta, Indonesia

Abstract

Background: Pneumonia can easily mimic malignancies. Pulmonary nodule findings raise concern for lung cancer. A single lung opacity less than 3 centimeters in diameter is referred to as a solitary pulmonary nodule (SPN). These nodules are sometimes incidentally discovered during routine computed tomography (CT) scans of the chest in relatively asymptomatic patients. We present an unusual case of pneumonia-like mass with spontaneous resolution.

Case: A woman, 38 years old, with a solitary pulmonary nodule which was found accidentally in the left lung upper lobe, without any respiratory symptoms in June 2021. In August 2021, a chest CT scan was done for evaluation and the solitary nodule of the left lung upper lobe had resolved spontaneously without any treatment. The patient was prepared for diagnostic bronchoscopy at Persahabatan Hospital with the findings of normal bronchi and branches. A bronchial washing was performed on the left B1+2 segment and cytology, fungal, microorganism and molecular tuberculosis examination were performed.

Discussion: Pulmonary solitary nodule in left lung upper lobe in the beginning and spontaneous resolution after 2 months evaluation without any specific treatment, consider the period of pneumonia. Whenever a patient is found to have an SPN, it is essential to determine the patient's risk for malignancy. It is important to consider any pulmonary nodule to be malignant or not, and how it presents on CT Imaging.

Conclusion: Pulmonary nodules may be found during pneumonia and may resolve spontaneously. The possibility of malignancy must still be considered. Awareness of the condition from the history is important to help reassure the patient about the disease even before the diagnostic procedure was made.

Keywords: pneumonia, solitary nodule, spontaneous resolution

Corresponding Author:
Aisyah Ayu Safitri | Department of Pulmonology and Respiratoty Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Regional Hospital, Jakarta, Indonesia | aiyu.paru@gmail.com

Submitted: September 21st, 2021
Accepted: April 10th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 221–3
https://doi.org/10.36497/jri.v43i3.205

INTRODUCTION

Pneumonia is an acute lung parenchyma infection with presenting symptoms are cough, pleuritic chest pain, fatigue and loss of appetite. The characteristic of pneumonia is the involvement of the alveolar cavity, the more distal the infection, the greater the probability of bacterial infection, and the more severe the degree of disease.[1]

Community-acquired pneumonia (CAP) can affect all age groups and is not always caused by bacteria but also by viruses or mechanical ventilation. Clinical assessment for disease history and physical examination is needed to determine the diagnosis. Risk factors and infections that cause CAP include agricultural animals, acquired immune deficiency syndrome (AIDS), alcohol aspiration, chronic obstructive pulmonary disease (COPD), and influenza.[1,2] Infectious Disease Society of America (IDSA) 2016 guidelines for the diagnosis of pneumonia recommend that identification of consolidation in chest radiographs is a gold standard to confirm the diagnosis. Other guidelines based on the British thoracic society (BTS) recommend assessing the full clinical picture in establishing the diagnosis of pneumonia. Patients with clinical pneumonia but no radiological abnormalities are recommended to repeat radiological imaging within the next 24–28 hours because one in 10 cases will develop radiographic evidence of pneumonia in the first 72 hours.[1]

A solitary pulmonary nodule (SPN) was defined as a round opacity with a diameter of 3 cm that was found incidentally on radiological imaging. Benign SPN includes infectious granulomas and hamartomas while malignant nodules include lung cancer, carcinoid tumors and pulmonary metastases.[3] These nodules pose diagnostic

sometimes incidentally discovered during routine CT scans of the chest in relatively asymptomatic patients. We present an unusual case of pneumonia-like mass with spontaneous resolution.

CASE

A 38-year-old woman was referred from the ENT clinic with a diagnosis of esophageal achalasia. The main complaint is difficulty swallowing since 4 years ago followed by weight loss of 26 kilograms in 4 years. The patient did not have symptoms of shortness of breath, cough, chest pain, fever or night sweats. The patient had no history of tuberculosis infection or previous history of cancer. A chest CT scan was taken on June 2021, it was found accidentally that there was a solitary nodule in the left lung upper lobe.

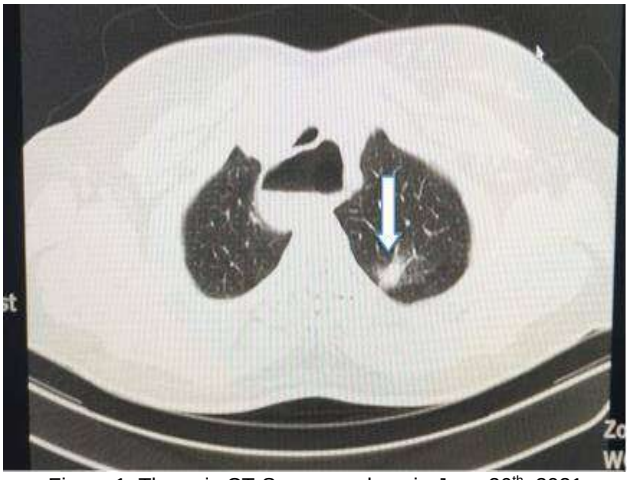

Figure 1. Thoracic CT-Scan was done in June 26th, 2021

The patient was prepared for diagnostic bronchoscopy and transbronchial lung biopsy at Persahabatan Hospital as a suspect solitary pulmonary nodule due to malignancy. In August 2021, an evaluating CT scan was performed for evaluating and the solitary nodule of the left lung upper lobe had resolved spontaneously without any specific treatment. The patient has been scheduled for a bronchoscopy procedure in September 2021. A bronchoscopy was performed on September 10th, 2021 with the findings of normal bronchi and the branches. A bronchial washing was performed in the left B1+2 segment and the specimen was examined for cytology, fungal, microorganism and molecular tuberculosis.

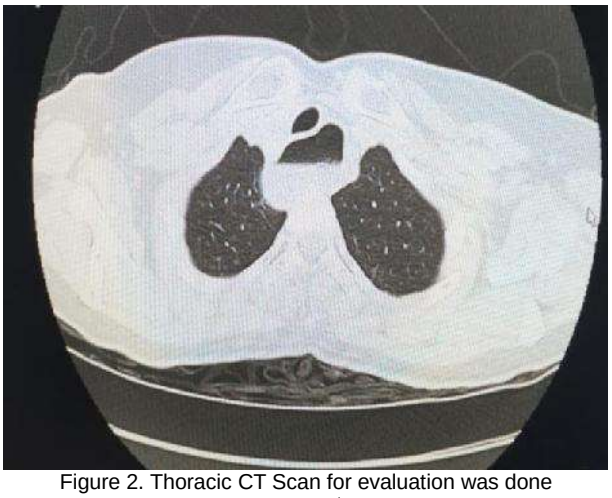

Figure 2. Thoracic CT Scan for evaluation was done in August 31st, 2021

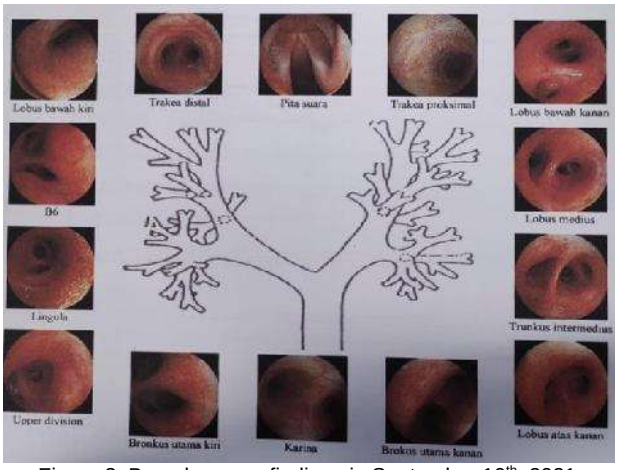

Figure 3. Bronchoscopy findings in September 10th, 2021

DISCUSSION

It is not easy to diagnose pneumonia. Anatomically, pneumonia is classified as bronchopneumonia or lobar pneumonia. Bronchopneumonia occurs when infection results in multifocal consolidation of the lung, while lobar pneumonia occurs when the area of consolidation is confined to the infected lobe. The differential diagnosis of pneumonia including pulmonary embolism, malignancy, or acute respiratory distress syndrome should be excluded. Identification of chest radiographic consolidation is the gold standard for radiological examination for the diagnosis of pneumonia, either on chest X-ray or chest CT scan. It is said that one-third of patients with pneumonia findings on chest X-ray do not have pneumonia findings on chest CT-Scan. [2,3]

Radiologic findings suggesting lung cancer include a parenchymal mass but are not specific to

lung cancer and non-malignant disease because of similar radiological findings.[4] The differential diagnosis should be made according to the presentation of signs and symptoms and radiologic finding evaluation. Pulmonary infections can easily mimic malignancy and tissue sample examination is required for a definitive diagnosis. Most primary malignant nodules are located in the upper lobes of the lung and two-thirds of metastatic lung nodules involve the lower lobes.[3]

In this report, the case in which the patient had a pulmonary solitary nodule in the left lung upper lobe in the beginning and spontaneous resolution after 2 months of evaluation without any specific treatment, considers the period of pneumonia. Whenever a patient is found to have an SPN, it is essential to determine the patient's risk for malignancy. It is important to consider whether any pulmonary nodule is malignant or not, and how it presents on CT Imaging.[5–7]

Some guidelines have detailed approaches for different types of nodules to distinguish between benign lesions and malignant nodules. Another case report shows a pulmonary nodule in metastatic renal cell carcinoma that resolved spontaneously without systemic steroid treatment, suggested mechanism is considered to be an immune response that may be evoked by surgery.[5–7]

LIMITATION

There are limitations in this case report. There were no data about sputum smear from this patient. The definitive cause of the nodule cannot be specified.

CONCLUSION

We described a 38-year-old woman with a pulmonary nodule in the left upper lobe which might be found during pneumonia with spontaneous resolution. The likelihood of malignancy must always be kept in mind. Awareness of the condition from the history is important to help reassure the patient about the disease even before the diagnostic procedure was made.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Grief SN, Loza JK. Guidelines for the evaluation and treatment of pneumonia. Prim Care. 2018;45(3):485–503.
2. Lim WS. Pneumonia—Overview. Encyclopedia of Respiratory Medicine. 2022;4:185–97.
3. Fernandes S, Williams G, Williams E, Ehrlich K, Stone J, Finlayson N, et al. Solitary pulmonary nodule imaging approaches and the role of optical fibre-based technologies. Eur Respir J. 2021;57(3):2002537.
4. Evman S, Bostanci K, Yuksel M. Infection or malignancy? Malignant pulmonary mass mimicking pneumonia. The Surgery Journal. 2016;2(1):e11–3.
5. Yuan DM, Zhang JY, Yao YW, Sun HM, Wu GN, Cao EH, et al. The pulmonary nodule "discovered" by pneumonia: a case report. Transl Lung Cancer Res. 2017;6(1):92–6.
6. Ueda K, Suekane S, Mitani T, Chikui K, Ejima K, Suyama S, et al. Spontaneous regression of multiple pulmonary nodules in a patient with unclassified renal cell carcinoma following laparoscopic partial nephrectomy: A case report. Mol Clin Oncol. 2016;5(1):49–52.
7. Kalanjeri S, Suri A, Wang H, Stover D. Lipoid pneumonia mimicking lung cancer. Chest. 2013;144(4):905A.

Case Report

Primary Spontaneous Pneumothorax in Healthy Tall and Thin Male Secondary to Smoking: A Case Report and Literature Review

Budi Yanti,[1,2] Rina Marlena[1,2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
[2]Department of Pulmonology and Respiratory Medicine, Zainoel Abidin General Hospital, Banda Aceh, Indonesia

Abstract

Background: Primary Spontaneous Pneumothorax (PSP) refers to the collapse of a lung without any underlying disease and is commonly observed in tall, thin young men, with smoking as an under-recognized risk factor. The management of PSP can vary significantly across different health centers. This case report highlights a young man with a pneumothorax without an underlying illness but has a smoking habit who initially gets treatment with an insertion of a chest tube.

Case: This study focused on a 19-year-old man complaining of sudden right chest pain. The patient was a smoker for the past four years, and the examination showed hypersonic and vesicular loss on the right side. The laboratory tests revealed normal limits, and the sputum indicated the absence of tuberculosis. Chest X-ray showed an avascular radiolucent area in the right lung, and a Chest CT scan confirmed the presence of a hypodense area of air density in the right hemithorax. Right PSP was diagnosed and managed using a chest tube drainage on admission. After four days of treatment, he exhibited improvement and was discharged. A recurrence of pneumothorax was not discovered in the subsequent six-month follow-up period.

Conclusion: Despite being a rare disorder, PSP should be considered during the physical examination of patients. It is also important to reassess the risk factors that can contribute to the onset of pneumothorax. The clinicians should be able to identify PSP and emphasize tall, thin, and young men at greater risk of pneumothorax in a pulmonary emergency.

Keywords: pulmonary emergencies, smoking, spontaneous pneumothorax, young

Corresponding Author:
Budi Yanti | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, Zainoel Abiding Teaching Hospital, Banda Aceh, Indonesia | byantipulmonologis@usk.ac.id

Submitted: May 30th, 2023
Accepted: June 8th, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 224–230
https://doi.org/10.36497/jri.v43i3.554

INTRODUCTION

The presence of pleural cavity air characterizes pneumothorax, located between the chest wall and the lungs. Furthermore, it can occur due to various factors, such as spontaneous leakage in the lung parenchyma or as a secondary effect of underlying diseases.[1] This condition can be further divided into two categories based on its cause: PSP and secondary spontaneous pneumothorax (SPP).[2]

Primary spontaneous pneumothorax refers to cases where pneumothorax transpires without an underlying lung disease. It is commonly observed in medical practice, particularly among young adults and adolescents with no preexisting condition or triggering event. PSP is commonly found in tall, young, and thin men and is often attributed to the rupture of blebs or bullae in the pleura.[2] The incidence of this condition varies based on gender and age, ranging from 7.4–18 and 1.2–6 cases per 100,000 population annually in men and women, respectively.[3]

The rupture of subpleural blebs or bullae in the apical segment of the upper or lower lobe is linked to the most frequent PSP mechanism. Smoking has been identified as the most significant risk factor, and the amount of cigarettes smoked daily increases the possibility of the condition. Furthermore, smoking can induce bronchial abnormalities, such as inflammation or obstruction in the distal airways, which contribute to the development of blebs in the lung parenchyma adjacent to the pleura.[4]

This study presents the condition of a 19-year-old man who reported chest discomfort lasting for the past 24 hours and a 4-year smoking history. Furthermore, this case highlights the importance of early detection and initial management of PSP in the absence of an evident cause. Complete resolution was achieved in the patient through timely

intervention, thereby preventing complications that can affect the quality of life in the future and facilitating an earlier return to physical activities.

CASE

A 19-year-old man came to the emergency room with right-sided chest pain, which started one day before hospitalization. The pain was described as a pressure-like sensation, not influenced by activity. Furthermore, the patient did not complain of shortness of breath but discomfort when breathing for the past day.

Further examination revealed the absence of restlessness, but there had been coughing without sputum for the past three days. There was no fever, loss of appetite, weight loss, night sweats, or previous medical history. A family history of allergies was denied, and no previous medication was used. The patient was a student with a height of 172 cm and a weight of 55 kg (body mass index 18.9 or within the normal range). There was a history of smoking for the past four years with a mild Brinkman index but no consumption of marijuana, illicit drugs, or alcohol.

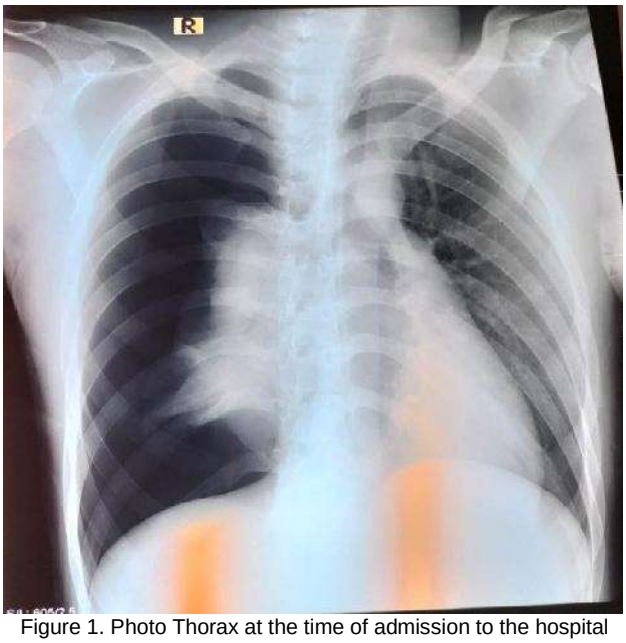

Figure 1. Photo Thorax at the time of admission to the hospital

On physical examination, the patient appeared calm with an average level of consciousness, 125/82 mmHg blood pressure, 98 beats per minute heart rate, 24 breaths per minute respiratory rate and 37.0°C temperature. During a pulmonary examination, hyper resonance on percussion and decreased vesicular breath sounds were observed in the right hemithorax. Laboratory tests at Dr. Zainoel Abidin General Hospital revealed 15.8 g/dL Hemoglobin, 46% Hematocrit, 8,400/mm^3 Leukocytes, 350,000/mm^3 Platelets, 3% Eosinophils, 0% Basophils, 0% Band neutrophils, 57% Segmented neutrophils, 31% Lymphocytes, 9% Monocytes, 11 mg/dL Urea, 0.9 mg/dL Creatinine, 14.10 seconds Prothrombin time (PT), 20.10 seconds activated partial thromboplastin time (aPTT). Furthermore, sputum testing using Rapid Molecular Test showed MTB (Mycobacterium tuberculosis) Not Detected. Chest X-ray revealed a right lung collapse with a large radiolucent area in the right hemithorax, as shown in Figure 1.

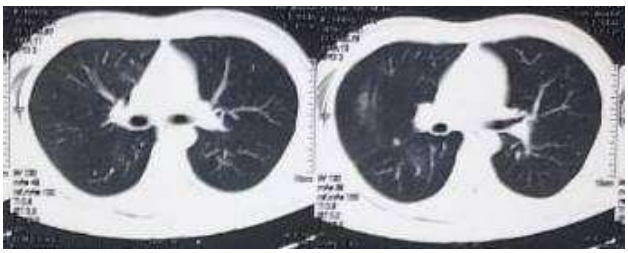

Figure 2. Thoracic CT Scan after chest tube performed

Furthermore, a thoracic CT scan showed a hypodense area with air density in the right hemithorax, as shown in Figure 2. Based on these findings, the patient was diagnosed with right-sided primary spontaneous pneumothorax.

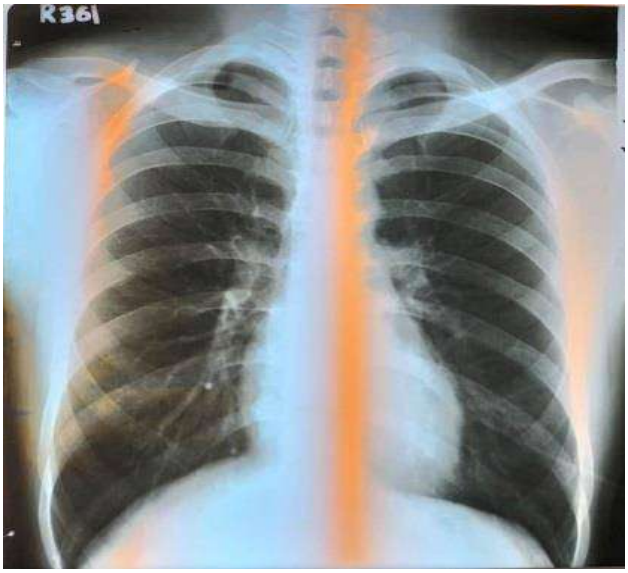

Figure 3. Photo Thorax at the time of discharge from the hospital

The patient was treated with a chest tube connected with water-sealed drainage (WSD) in the

right hemithorax to remove air from the pleural cavity. After four days of treatment, with no further fluctuations observed in the WSD, a physical examination revealed the presence of vesicular breath sounds in the right and left lungs. The chest X-ray showed the absence of a collapsed line in the right lung. Subsequently, the patient was discharged in a healed condition, as shown in Figure 3.

The patient was followed up for six months, and clinical evaluation showed no symptoms or signs of recurrent pneumothorax. A chest X-ray evaluation was performed, and the results showed that the lung and heart conditions were within normal limits, as shown in Figure 4.

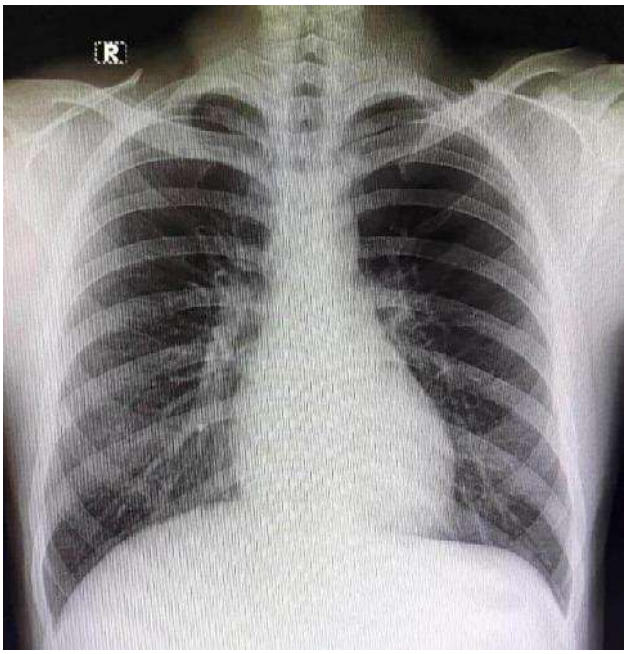

Figure 4. Follow-up photo thorax after six months

DISCUSSION

In this case, there was significant uncertainty regarding the air source in the right pleural cavity at hospitalization. Furthermore, on chest X-ray, most cases of sudden-onset pneumothorax in the thorax did not show any visible fractures in the chest wall. Although there were suspicions of a ruptured bleb due to the patient's smoking habit for the past four years, it was difficult to confirm this condition. The chest X-ray confirmed the initial suspicion, and the CT scan findings showed a case of PSP.

Primary spontaneous pneumothorax has an incidence rate of 7.4–18 cases per 100,000 people per year in males and 1.2–6 cases in females. It often occurs in males, individuals with a tall body posture, and frequent smokers. PSP could also occur at rest, removing the need to avoid physical activity. Spontaneous pneumothorax in patients with underlying lung disease is classified as secondary spontaneous pneumothorax (SSP). This classification is made because they have differences in prognosis and management.[5]

Patients with PSP often complain of sharp ipsilateral chest pain and mild dyspnea. Furthermore, the physical examination findings depend on the air volume in the pleural cavity. In this condition, breath sounds are often decreased or absent, with hyper-resonant percussion. The most common cause of spontaneous pneumothorax is the rupture of subpleural blebs or lung bullae.[6] Upon the suspicion of pneumothorax, the patient must be taken to a medical care center, and a chest X-ray is mandatory as the initial diagnostic examination.[7]

The first step in managing this condition is deciding on the necessary intervention or whether the patient could be managed conservatively with observation alone. The British Thoracic Surgery (BTS) recommends using various treatment methods in patients with large or symptomatic pneumothorax. BTS defines a large pneumothorax as >2 cm measured from the visceral pleura visible on the lateral chest wall at the level of the hilum on chest X-ray. Furthermore, it is recommended that in some patients with this type but minimal symptoms, conservative management could be pursued.[8] In this case, a large pneumothorax with dyspnea symptoms was found. The patient was then followed up with a chest tube intervention to drain air from the pleural cavity and reduce dyspnea.

Some patients with small pneumothorax (<15% of total lung volume) could only be observed without needing hospitalization.[9] However, further chest X-rays are needed to assess the potential expansion of the condition. If there was no progression and the vital signs were stable, the patient could be safely discharged home. Weekly chest X-ray evaluations must also be performed until complete resolution,

usually within two weeks. If air leakage persisted with progressive collapse or unresolved pneumothorax, a chest tube procedure was an alternative treatment option. Feden et al. suggested that in cases where the pneumothorax was >20% of total lung volume, or the patient exhibited unstable vital signs, immediate admission to the hospital emergency room and evacuation of air from the pleural cavity with a chest tube must be performed.[10]

Spontaneous pneumothorax could occur without prior trauma or iatrogenic injury. Therefore, the air in the pleural cavity could originate from the connection between the alveolar space containing air from the lung and the pleural cavity.[11] Although PSP was generally considered to occur without underlying lung disease, there was ample evidence to suggest that it had a minor locus in the lung.[12] Several references indicate some risk factors were associated with PSP, such as Body Mass Index (BMI); smoking; bleb and bullae; microscopic abnormalities, inflammation; pleural porosity; abnormal elastolysis; and hereditary disorders

Body Mass Index

Primary spontaneous pneumothorax occurred more frequently in tall, thin patients with low BMI and smokers. After the first episode, the risk of recurrence in PSP patients was higher than in tall individuals.[13] Primary spontaneous pneumothorax patients were frequently ectomorphic (tall and slender) from childhood on, but between the ages of 11 and 14, there were noticeable height increases relative to national standard values. According to numerous investigations, the pleural pressure increased from the base to the apex of the lung. Therefore, levels in the lung apex were higher in people with tall stature. The pressure causes this condition had a high correlation with surface area, and increased levels in the apex tended to cause the formation of blebs and bullae.[3]

Based on previous studies, triggering factors for increased intrapleural pressure could be attributed to changes in atmospheric pressure, physical activity, and exposure to loud music, leading to acute changes in transpulmonary pressure due to sound energy exposure.[14]

Smoking

Tobacco smoking remained the most critical risk factor for PSP. A retrospective study in Stockholm assessed the smoking rates of 138 patients hospitalized over ten years and compared them with a large contemporary random sample. The results showed that 88% of PSP cases occurred in people with positive smoking status. Compared to non-smokers, the relative risk of spontaneous pneumothorax increased by ninefold in women and 22-fold in men who smoked. Furthermore, there was a strong dose-response relationship between the risk of pneumothorax occurrence and the number of cigarettes smoked daily. Minor airway abnormalities stimulated by smoking (cigarette smoke) could lead to the development of subpleural blebs.[15]

Bleb and Bullae

Blebs and bullae were known as emphysema-like changes (ELC). Blebs are tiny, air-filled sacs or vesicles of the visceral pleura brought on by air in the interstitial space. It typically had a diameter of about 1 cm and was frequently developed between the pulmonary pleura's internal and exterior elastic lamina. Bullae, or subpleural emphysematous bullae, on the other hand, were more oversized air pockets that were >1 cm and were strongly marked by thin walls (1 mm).[16]

Microscopic Abnormalities, Inflammation

Microscopic evaluation of the lung tissue from PSP patients with lung excision revealed fibrotic changes and persistent distal airway damage with lymphocyte and macrophage infiltrating. Furthermore, in apparently healthy lungs, persistent inflammation may result in the development of ELC.[17]

Pleural Porosity

The concept of pleural porosity involves air leakage from the alveoli into the pleural cavity through thin pores in the visceral pleura.[18] In some

cases, including this current patient, no macroscopic lesions were found based on CT scans. Furthermore, this supported the suspicion of pleural porosity as the cause of PSP when air leaked from the thinned visceral pleura, not just from blebs or bullae.

Several studies have been carried out to compare autofluorescence thoracoscopy in 12 PSP patients and 17 healthy subjects who underwent sympathectomy and had no lung disease or previous pneumothorax. Based on previous studies, fluorescein was known to emit green fluorescence under ultraviolet light. Before the procedure, patients were asked to inhale nebulized fluorescein, and subpleural green fluorescence was found under ultraviolet light in the peripheral lung area. This result indicated that the inhaled substance approached the lung surface, a typical condition in thoracoscopy. The last regular lesions were found in PSP patients with ELC, indicating the occurrence of air leakages at the sites of blebs or bullae macroscopically.

Abnormal Elastolysis

Elastolysis refers to the imbalanced degradation of elastic fibers in the lungs, causing the tissues to become more "fragile. The degeneration of elastic fibers and the developing porous elastofibrotic layers could result from chronic peripheral airway inflammation. Additionally, there was proof of a disparity between the oxidant-antioxidant mechanism and the protease-antiprotease pathway. Endopeptidases known as matrix metalloproteinases (MMPs) could rupture the barrier separating the pulmonary cells from the alveoli. In addition to asthma and COPD, MMP-2 and MMP-9 were thought to be harmful in various lung conditions.[19]

Immunohistochemistry on the pulmonary tissues revealed elevated MMP-2, 7, and 9 expressions in PSP cases. In 91 pneumothorax subjects, some studies also discovered the elevated expression of MMP-2 and MMP-9. Furthermore, individuals with recurrent pneumothorax episodes were reported to have increased expression of MMP. Apart from the exaggerated expression of MMPs potentially damaging lung tissue, protective factors are also depleted, leading to increased fragility of the lung tissue.

Hereditary Disorders

Based on previous reports, several hereditary conditions were associated with a tendency to pneumothorax, such as connective tissue diseases (Marfan syndrome, Ehlers-Danlos syndrome, or other mutations of the folliculin gene), defects with cystic patterns or emphysema development (Birt-Hogg-Dube syndrome (BHD), alpha-1 antitrypsin deficiency), and metabolic conditions (such as Homocystinuria). Although uncommon, people with a family record of accidental pneumothorax frequently needed additional testing since episodes of spontaneous pneumothorax may be a sign of these genetic disorders.[20]

Treatment for PSP patients had two goals: air evacuation and preventing recurrence, as well as avoiding complications, such as trapped lung due to thickening of the visceral pleura.[21,22]

1. Conservative

   The observation could be performed for patients with minimal or no symptoms, with easy access to the medical care available in case of worsening, leading to lung collapse.
2. Pleural Aspiration or Chest Tube Drainage.

   Aspiration could be used as initial management for PSP patients, specifically in younger patients (<50 years old) with moderate-sized secondary pneumothorax (1-2 cm in size). The rate of pneumothorax recurrence after aspiration was nearly the same as after chest tube insertion. Furthermore, chest tube insertion was the thorax's most commonly performed surgical procedure. This procedure was often performed to re-expand the collapsed lung (lung re-expansion).
3. Pleurodesis

   Pleurodesis was aimed to create adhesion between the visceral and parietal pleura to prevent the recurrence of pneumothorax. It was often carried out by instilling irritant chemicals (chemical pleurodesis) or performing cart mechanical abrasion (mechanical pleurodesis) and parietal

pleurectomy. Based on previous studies, talc poudrage was Europe's most commonly used method due to its cost-effectiveness. It could be used to achieve the desired diffuse chemical pleurodesis to prevent PSP recurrence. However, there were some limitations, such as in cases of visceral pleural rupture, where immediate referral for resection of the leaking lung parenchyma was recommended.

4. Video-assisted thoracoscopy (VATS)

   VATS allowed minimally invasive access to the pleural cavity and was preferred over open thoracotomy for pneumothorax management.

LIMITATIONS

This case does not represent a severe pneumothorax. Therefore it does not show additional methods that can be employed to manage a severe pneumothorax. Instead, it describes a patient with a mild to moderate spontaneous pneumothorax that could be treated by inserting a chest tube. Nevertheless, this investigation will effectively aid patients' management strategies and compare various PSP therapy strategies.

CONCLUSION

Primary spontaneous pneumothorax commonly occurs in young, tall, thin men with stable clinical presentations, often with mild chest pain complaints. Various diagnostic tests had been performed in this case, and the results were typical. Furthermore, a history of smoking was the only risk factor that triggered PSP in this patient. Conservative management could be considered for small PSPs measuring less than 20%, while chest tube placement is recommended for larger pneumothoraces. This patient in this study was treated using definitive management involving a chest tube, which re-expanded the lung without recurrence.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Čolić T, Leljak LČ, Žganjer M, Stipić D. Treatment of primary spontaneous pneumothorax in pediatric patients: 15-yeas experience at a single-institution. Acta Chirurgica Croatica. 2020;17:17–20.
2. Stodghill JD, Collins DT, Mahajan AK, Khandhar SJ. Primary spontaneous pneumothorax: A pathway to practice. AME Med J. 2019;4:8.
3. Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. European Respiratory Review. 2010;19(117):217–9.
4. Ghisalberti M, Guerrera F, De Vico A, Bertolaccini L, De Palma A, Fiorelli A, et al. Age and clinical presentation for primary spontaneous pneumothorax. Heart Lung Circ. 2020;29(11):1648–55.
5. Maglica M, Jurčević A, Jurčević B, Mišković J. Spontaneous pneumothorax in a young male athlete: A case report with review of literature. Indian Journal of Case Reports. 2023;9(1):26–8.
6. Hallifax R. Aetiology of primary spontaneous pneumothorax. J Clin Med. 2022;11(3):490.
7. Chaturvedi A, Lee S, Klionsky N, Chaturvedi A. Demystifying the persistent pneumothorax: role of imaging. Insights Imaging. 2016;7(3):411–29.
8. MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2(SUPPL. 2).
9. Hallifax RJ, Roberts M, Russell N, Laskawiec-Szkonter M, Walker SP, Maskell NA, et al. Pneumothorax management: current state of practice in the UK. Respir Res. 2022;23:23.
10. Feden JP. Closed lung trauma. Clin Sports Med. 2013;32(2):255–65.

11. Gilday C, Odunayo A, Hespel AM. Spontaneous pneumothorax: Pathophysiology, clinical presentation and diagnosis. Top Companion Anim Med. 2021;45:100563.
12. Wilson PM, Rymeski B, Xu X, Hardie W. An evidence-based review of primary spontaneous pneumothorax in the adolescent population. J Am Coll Emerg Physicians Open. 2021;2(3):e12449.
13. Tan J, Yang Y, Zhong J, Zuo C, Tang H, Zhao H, et al. Association between BMI and recurrence of primary spontaneous pneumothorax. World J Surg. 2017;41(5):1274–80.
14. Noppen M, Verbanck S, Harvey J, Van Herreweghe R, Meysman M, Vincken W, et al. Music: a new cause of primary spontaneous pneumothorax. Thorax. 2004;59(8):722–4.
15. Cheng YL, Huang TW, Lin CK, Lee SC, Tzao C, Chen JC, et al. The impact of smoking in primary spontaneous pneumothorax. J Thorac Cardiovasc Surg. 2009;138(1):192–5.
16. Choi W Il. Pneumothorax. Tuberc Respir Dis (Seoul). 2014;76(3):99–104.
17. Lyra R de M. A etiologia do pneumotórax espontâneo primário. Jornal Brasileiro de Pneumologia. 2016;42(3):222–6.
18. Haynes D, Baumann MH. Pleural controversy: aetiology of pneumothorax. Respirology. 2011;16(4):604–10.
19. Gupta R, Patail H, Al-Ajam M. A rare case of bronchial elastosis: An unusual presentation of an unexpandable lung. Lung India. 2018;35(1):50–3.
20. Boone PM, Scott RM, Marciniak SJ, Henske EP, Raby BA. The genetics of pneumothorax. Am J Respir Crit Care Med. 2019;199(11):1344–57.
21. Vallejo FAG, Romero R, Mejia M, Quijano E. Primary spontaneous pneumothorax, a clinical challenge. Amer K, editor. Pneumothorax. 2019;Ch. 2.
22. Tschopp JM, Bintcliffe O, Astoul P, Canalis E, Driesen P, Janssen J, et al. ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. European Respiratory Journal. 2015;46(2):321–35.

AUTHORS INDEX

SUBJECTS INDEX