VOL. 42, NO. 4, October 2022

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 42, NUMBER 4, October 2022

TABLE OF CONTENT

Original Article

Literature Review

Original Article

Combined Upper Limb Exercise and Creatine Monohydrate Supplementation Improved Musculoskeletal Function in NSCLC Patients

Muhammad Addinul Huda, Ana Rima Setijadi, Reviono, Farih Raharjo, Yusup Subagio Sutanto

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

Abstract

Background: Lung cancer is a chronic respiratory disease that causes muscle dysfunction. Giving creatine monohydrate supplementation combined with exercise has efficacy in increasing lean body mass (LBM), muscle strength, and physical function. This study aims to analyze the effect of a combination of creatine monohydrate supplementation and upper limb exercise on skeletal muscle dysfunction in NSCLC patients.

Methods: A quasi-experimental study with a pretest-posttest study on NSCLC patients given epidermal growth factor receptor (EGFR) – tyrosine kinase inhibitors (TKIs) from outpatient at RSUD Dr. Moewardi Surakarta in September - October 2021. The combination group of creatine monohydrate supplementation with upper limb exercise (n=15), the group with creatine monohydrate supplementation only (n=16), and the control group (n=15). Lean body mass in kilograms and percentages, 6-minute walk test (6MWT), and quality of life were assessed after 8 weeks of treatment.

Results: The increase in LBM in the combination group was 4.22±1.81kg and 6.38±2.48% (*P*=0.0001). The combination groups have a greater increase in the 6MWT was 104±20.07 meters. The increase in quality of life in the combined creatine monohydrate supplementation group with upper limb exercise was 20.80±10.75. Changes in the value of LBM, 6MWT, and quality of life (QoL) in the creatine monohydrate supplementation combined with upper limb exercise were significantly different compared to the creatine monohydrate supplementation only group and the control groups.

Conclusion: There is a greater effect of giving a combination of creatine monohydrate supplementation and upper limb exercise on LBM, 6MWT, and QoL in NSCLC patients.

Keywords: 6MWT, creatine, exercise, LBM, NSCLC, QoL

Corresponding Author:
Muhammad Addinul Huda | Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital, Surakarta, Indonesia | nulhudahlan@gmail.com

Submitted: April 27th, 2022
Accepted: August 5th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 257–67
https://doi.org/10.36497/jri.v42i4.310

INTRODUCTION

New cases of lung cancer in Indonesia increased more than five times in the last ten years.[1,2] Most patients with NSCLC adenocarcinoma-type have sensitization mutation in exon 19 or 21 (about 45 and 40% of patients, respectively) that activates the tyrosine kinase domain in the EGFR receptor especially among Asians because it has a higher prevalence of EGFR mutations compared to Caucasians. The use of EGFR-TKI as a first-line treatment has shown a longer progression-free survival (PFS), improved health-related quality of life, and lower side effects treatment-related when compared with standard chemotherapy.[3]

Lung cancer is a chronic respiratory disease that causes impaired ventilation that causes physical inactivation. Cancer patients are exposed to various specific cancer factors that result in the loss of mass and function of muscle, like factor-related to tumor cancer therapy, malnutrition, lack of physical activity, age, and comorbidities. Compensation to reduce symptoms of shortness of breath and fatigue by reducing activity resulting in muscle atrophy so that the vicious cycle keeps progressing and explains the connection between physical inactivation and worsening of symptoms.[4,5] Muscle atrophy contributes to weakness, decreased mobility, and fatigue in cachectic patients and could increase the risk of respiratory failure as a common cause of death from cancer.

Cancer-related muscle dysfunction is defined as a measurable disturbance in muscle strength or muscle composition. The degree of muscle

dysfunction can be measured from muscle strength and muscle composition in the form of lean body mass.[6,7] Upper extremity muscles are very important for manipulating objects and for personal care and affect the quality of life. Muscle strength also depends on muscle mass, length, innervation, size, and fiber type.[8]

Walking is a usual activity for all patients except for those with severe disorders. The American thoracic society (2002) recommends the 6-minute walk test to measure the response of therapeutic interventions for cardiorespiratory disease.[9]

Abnormalities of body composition affect all chronic lung diseases. Measuring body mass index (BMI) does not accurately reflect body composition changes like fat-free mass (FFM) which consists of bone, muscle, vital organs, and extracellular fluid. Lean body mass (LBM) differs from FFM in the form of lipid in the cellular membranes that are included in the LBM but only a small fraction or as much as 3–5% of the total body weight.[10,11]

Muscle mass is maintained by the balance between protein synthesis and breakdown, called protein turnover. Impaired ventilation due to lung cancer causes hypoxemia resulting in anaerobic metabolism. Lactate from anaerobic metabolism is increased and partially converted into glucose through the Cori cycle which requires adenosine triphosphate (ATP), causing a decrease in energy which results in muscle dysfunction. Muscle atrophy due to cancer occurs as a result of an increased inactivation of protein breakdown and suppression of protein synthesis.[12] Data on muscle mass were assessed by dual-energy X-ray absorptiometry (DXA) scan and bioelectrical impedance.

Creatine monohydrate (Cr) is one of the most researched supplements that has efficacy in increasing lean body mass, muscle strength, and physical function.[13,14] Creatine plays an important role to supply rapid energy during muscle contraction which involves the transfer of a phosphoryl group from phosphocreatine (PCr) to adenosine diphosphate (ADP) for regeneration of adenosine triphosphate (ATP) through a reversible reaction catalyzed by phosphocreatine kinase (PCK). Creatine is responsible for the transfer of energy from the mitochondria to the cytosol.[14–16]

Exercise training in chronic respiratory conditions is to optimize lung function in daily activities. The standard pulmonary rehabilitation protocol consists of three sessions of 30 to 90 minutes per week for 6 to 8 weeks consisting of individual aerobic exercise and strength training.[17,18]

Muscle strength resistance training involves specific muscle groups by lifting or pushing weights repeatedly. The American Thoracic Society/European Respiratory Society (ATS/ERS) for lungs rehabilitation recommend two set of 6–12 reps, gradually increased, a maximum of two to three times per week.[10,17,19]

Non-pharmacological modalities of therapy in lung cancer patients are still not widely studied. This study aims to determine the effect of the combination of creatine monohydrate supplementation and upper limb exercise in improving skeletal muscle dysfunction and improving the quality of life in NSCLC patients.

METHODS

Quasi-experiment studies with pretest and post-test control group designs were done to evaluate the lean body mass (kg), lean body mass (%), 6-minute walk test, and quality of life. The study was carried out at Dr. Moewardi Surakarta from September 2021 to November 2021. The study population was NSCLC patients with EGFR TKI at RSUD Dr. Moewardi Surakarta using consecutive sampling. The research subjects were grouped into the treatment group with the combination of creatine monohydrate supplementation with upper limb exercise as first group, creatine monohydrate supplementation only as second group, and the control group or third group. Subjects measured the lean body mass with a bioelectrical impedance scale, 6-minutes walking test, and quality of life using a Fact-L questionnaire.

The first group received an education on how to take creatine monohydrate supplementation and

was taught about upper limb exercise. Creatine supplementation monohydrate as much as 5 grams (1 teaspoon) dissolved in 250 ml drinking water and consumed once a day. The upper limb exercise is carried out in a sitting position by holding a bottle filled with 600 mL of water then performing elbow flexion and extension movements to train the biceps and triceps muscles, abduction, and adduction movements of the upper arms to train the deltoids. The movement is continued by bending the body slightly then raising both hands and bringing them together behind the neck. The next movement is in a lying position and moving both hands ahead. Each set of movements is done for 12 repetitions and repeated up to 5 sets. Upper limb exercise sessions are carried out every day.

The supplementation group only received education on how to take the same amount of creatine monohydrate supplementation without giving upper limb exercise treatment. The control group was not given any non-pharmaceutical treatment. All forms of treatment are given every day for 8 weeks. Evaluation of lean body mass, 6-minute walk test, and quality of life were measured again after 8 weeks. The number of samples required is 15 samples per group.

Inclusion criteria of this study are stage IV NSCLC patients in hospital Dr. Moewardi Surakarta with targeted therapy for TKI EGFR at least on the second month, shows a minimum performance status (PS) of 70-80, the patient is willing to take part in the study by signing the informed consent, the patient's age is minimum 18 years, as well as patient, could read and write. The exclusion criteria of this study are patients with impaired consciousness, walking disorders, upper extremity activity disorders, and patients with pneumonia. The criteria for the discontinuity of the study where the subjects did not perform the procedure for 14 days consecutive.

This research was approved by the Ethics Worthiness Committee of the RSDM/Faculty of Medicine, Sebelas Maret University, Surakarta in October 2021. All research data were carried out by the normality test of the distribution of research data. All research data were tested for the normality of research data using the normality Kolmogorov-Smirnov test. The value of $P>0.05$ means that the subjects in the study are homogeneous. A difference test is a statistical technique test used to see the difference between treatment samples. Statistical tests on the pre and post-test independent samples were tested using a paired t-test if the data distribution was normal. If the data distribution is not normal then the Mann-Whitney test is used. The next difference test is ANOVA to see the difference among the three groups if the data distribution is normal. If the data distribution is not normal, then used the Kruskal-Wallis test. The difference test among the 3 groups was continued with the Bonferroni post hoc test if the data were homogeneous and Games-Howell if the data are non-homogeneous. The limit of the mean if the value of $P\leq0.05$ means significant statistically.

RESULTS

This study was conducted at the Dr. Moewardi hospital Surakarta from September 2021 to October 2021. The eligible subjects were divided into three groups by consecutive sampling which is the combination group with creatine monohydrate supplementation with upper limb exercise, the group of creatine monohydrate supplementation only, and the control.

There are total 46 subjects recruited, but three of the subjects excluded due to death. Three subjects were discontinued in the study because the patient passed away. The subjects were then divided into 3 groups. The first group consisted of 15 NSCLC patients who received targeted therapy and creatine monohydrate supplementation combined with upper limb exercise. The second group consisted of 16 NSCLC patients who received targeted therapy and creatine monohydrate supplementation only. The third group was the control group, which consisted of 15 NSCLC patients who received targeted therapy. The research data collected were tabulated and then analyzed as follows.

Table 1. Characteristics of Subjects.

Characteristics	Group			*P*
	Group 1	Group 2	Group 3	
Sex				
Men	5 (10.9%)	5 (10.9%)	5 (10.9%)	0.99
Women	10 (21.7%)	11 (34.8%)	10 (21.7%)	
Age	60.7±7.43	58.1±8.16	53.1±14.17	0.135
Exon				
19	9 (19.6%)	10 (21.7%)	13 (28.3%)	0.213
21	6 (13%)	6 (13%)	2 (4.3%)	
Regimen targeted therapy				
Afatinib	11 (23.9%)	8 (17.4%)	8 (17.4%)	
Erlotinib	2 (4.3%)	3 (6.5%)	4 (8.7%)	0.611
Gefitinib	2 (4.3%)	5 (10.9%)	3 (6.5%)	
Duration therapy	10.4±9.62	11.06±6.77	13.27±9.03	0.631
Smoking history				
Smoker	3 (6.5%)	5 (10.9%)	4 (8.7%)	0.774
Non Smoker	12 (26.1%)	11 (23.9%)	11 (23.9%)	

Table 2. Characteristics of Variables

Variable	Group			*P*
	Group 1	Group 2	Group 3	
Lean body mass (pre) [kg]	34.0±7.16	32.23±6.33	36.53±9.55	0.313
Lean body mass (pre) [%]	74.24 ±5.19	72.15±8.76	69.17±8.11	0.192
Lean body mass (post) [kg]	38.24± 7.40	33.41±6.88	36.29±9.15	0.236
Lean body mass (post) [%]	80.63± 5.57	74.61±10.07	68.93±8.98	0.002*
6-minute walk test (pre)	225±72.39	206±69.23	223±76.69	0.729
6-minute walk test (post)	329±70.42	268±65.31	268±79.38	0.033*
Quality of life (pre)	86±20 7	85±20.9	96±14.6	0.199
Quality of life (post)	107±15 89	96±20.32	104±14.58	0.200

The research subjects are 46 NSCLC patients consisting of 15 men and 31 women (*P*=0.990). The average age in the combination group is 60.7±7.43 years, in the creatine monohydrate supplementation-only group is 58.1±8.16 years and in the control group 53.1±14.17 years (*P*=0.135).

Most of subjects 69.5% were having mutation exon 19 with 58.6% received Afatinib, 19.5% received Erlotinib, and 21.7% received Gefitinib (*P*=0.611). With average duration of EGFR TKI therapy was 10.4±9.62 months for first group, 11.06±6.77 months, and 13.27±9.03 months for the second and third group (*P*=0.631). There were 6.5% smokers in first group, 10.9% in second group, and 8.7% in third group (*P*=0.774). The basic characteristics of the research subjects can be seen in Table 1.

The variable analyzed in this study is lean body mass, 6MWT, and quality of life in patients with NSCLC. Lean body mass is assessed in kilograms (kg) and percent (%), a 6-minute walk test is assessed in meters, and quality of life is assessed by a FACT-L questionnaire in the form of total scores. The results of the different tests using one-way ANOVA on each variable showed that lean body mass and 6MWT after treatment had significant differences in all three groups, whereas the other variable showed no statistically significant difference. The characteristics of the variables can be seen in Table 2.

The average value of lean body mass in kg before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 34.01±7.16 kg; the creatine monohydrate supplementation group only was 32.23±6.33 kg, and the control group was 36.53±9.55 kg. Lean body mass average score after treatment on the combination of supplementation creatine monohydrate with upper limb exercise group was 38.24±7.40 kg, in the group supplementation creatine monohydrate only was

33.41±6.88 kg; and in the control group was 36.29±9.15 kg. There is significantly increase in lean body mass for first group 4.22±1.81 kg (*P*=0.0001). Second group 1.17±3.45 kg (*P*=0.192) and third group -0.24±1.87 kg (*P*=0.623).

Another assessment for lean body mass (%) was obtained from the total body weight. The average value of lean body mass (%) before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 74.24±5.19%; in the supplementation group creatine monohydrate is 72.15±8.76%, and in the control group is 69.17±8.11%.

Table 3. Lean body mass difference pair-test among groups

Groups	Lean body mass			*P*
	Pre	Post	Difference	
Group 1	34.01±7.16 kg	38.24±7.40 kg	4.22±1.81 kg	0.0001*
	74.24±5.19 %	80.63±5.57%	6.38±2.48%	0.0001*
Group 2	32.23±6.33 kg	33.41±6.88 kg	1.17±3.45 kg	0.192
	72.15±8.76%	74.61±10.07%	2.46±7.34%	0.200*
Group 3	36.53±9.55 kg	36.29±9.15 kg	-0.24±1.87 kg	0.623
	69.17±8.11%	68.93±8.98%	-0.23±2.32%	0.699

Table 4. Post hoc test results on changes in lean body mass

Variabel				Mean Difference	*P*
Lean Body Mass (kg)	Bonferroni	Group 1	Group 2	3.057	0.005*
			Group 3	4.494	0.0001*
		Group 2	Group 1	-3.057	0.005*
			Group 3	1.436	0.364
		Group 3	Group 1	-4.494	0.000*
			Group 2	-1.436	0.364
Lean Body Mass (%)	Games-Howell	Group 1	Group 2	3.9220	0.136
			Group 3	6.621	0.0001*
		Group 2	Group 1	-3.9220	0.136
			Group 3	2.699	0.363
		Group 3	Group 1	-6.621	0.0001*
			Group 2	-2.699	0.363

Table 5. Paired test of 6-minute walk test and Quality of Life

Variable		Pre	Post	Diff	*P*
6-minute walk test	Group 1	225±72.39	329±70.42	104±20.07	0.0001
	Group 2	206±69.23	268±65.31	62±28.69	0.0001
	Group 3	223±76.69	268±79.38	45±19.89	0.0001
Quality of life	Group 1	86±20.7	107±15.89	20.80±10.75	0.0001
	Group 2	85±20.9	96±20.32	10.62±7.30	0.0001
	Group 3	96±14.6	104±14.58	7.26±4.81	0.0001

Table 6. Post hoc test results on changes in 6MWT and Quality of life

Variable				Mean Difference	*P*
6MWT	Bonferroni	Group 1	Group 2	42.396	0.0001*
			Group 3	58.533	0.0001*
		Group 2	Group 1	-42.396	0.0001*
			Group 3	16.138	0.185
		Group 3	Group 1	-58.533	0.0001*
			Group 2	-16.138	0.185
Quality of life	Games-Howell	Group 1	Group 2	10.175	0.014*
			Group 3	13.533	0.001*
		Group 2	Group 1	-10.175	0.014*
			Group 3	3.358	0.298
		Group 3	Group 1	-13.533	0.001*
			Group 2	-3.358	0.298

The average value of lean body mass after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise obtained 80.63±5.57%; in the creatine monohydrate supplementation only group it was 74.61±10.07% and in the control group was 68.93±8.98%.

The difference in the addition of lean body mass in the first group was 6.38±2.48% (*P*=0.0001), 2.46±7.34% (*P*=0.200), and there is the decrease of lean body mass on group control -0.23±2.32% (*P*=0.699). The differences can be seen in Table 3.

The multivariate test showed *P*<0.05 means there was a significant difference between the three groups. The homogeneity test on lean body mass in kg (*P*=0.084), which means the data was homogeneous, so it continued with the post hoc Bonferroni test. The post hoc test results for lean body mass (kg) stated that the combination of creatine monohydrate supplementation with upper limb exercise was significantly different compared to the creatine monohydrate supplementation group and the control group.

Lean body mass in percentage data was homogenous (*P*=0.01), so analyzing continued with the Games-Howell post hoc test. The post hoc test results stated that the combination of creatine monohydrate supplementation with upper limb exercise was not significantly different compared to the creatine monohydrate supplementation group only but significantly different from the control.

The average value of the 6MWT before treatment in the combined creatine monohydrate supplementation group with upper limb exercise was 225±72.39 meters, in the creatine monohydrate supplementation group, only 206±69.23 meters, and in group control is 223±76.69 meters. The average value of the 6-minute walk test after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 329±70.42 meters, in the creatine monohydrate supplementation group only was 268±65.31 meters, and in the control group is 268±79.38 meters. The increase of the 6-minute walk test in the combination group of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation-only group, and control is 104±20.07 meters *P*=0.0001), 62±28.69 meters (*P*=0.0001), and 45±19.89 meters (*P*=0.0001) respectively.

The mean score of the quality of life before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise obtained 86±20.7; in the creatine monohydrate supplementation group only was 85±20.9, and in the control group was 96±14.6. The average value of quality of life after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 107±15.89; in the creatine monohydrate supplementation-only group was 96±20.32, and in the group control was 104±14.58. The difference in the addition of quality of life in the combination group of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation-only group, and control group each 20.80±10.75; 10.62±7.30; and 7.26±4.81 respectively in the three groups *P*=0.0001, which mean that there was a statistically significant change in the quality of life score.

Both of 6-minute walk test and quality of life have larger additions in the combination of creatine monohydrate supplementation with the upper limb exercise group compared to the creatine monohydrate supplementation-only group, and the control group. The change is statistically significant if *P*<0.05 occurred in the three groups. The differences can be seen in Table 5.

The statistical test for changes in the 6MWT and quality of life score was followed by the Kolmogorov-Smirnov test and continued with the homogeneity test. The homogeneity test on the 6MWT was found *P*=0.173, means that the data was homogeneous. The value of quality of life *P*=0.01, means that the data was not homogeneous. Both data followed by a multivariate test showed the value of *P*<0.05 meaning there was a significant difference in the three groups and followed by a

post hoc test Bonferroni for the 6MWT and Games-Howell for quality of life.

The post hoc test results stated that the combination of creatine monohydrate supplementation with upper limb exercise was significantly different compared to the creatine monohydrate supplementation group and the control group. The creatine monohydrate supplementation group only was not significantly different from the control group. It means combination groups have a superior effect on the 6MWT and quality of life. The results can be seen in Table 6.

DISCUSSION

This research is a quasi-experimental study to determine the effect of the combination of creatine monohydrate supplementation and upper limb exercise on muscle dysfunction and quality of life in patients with NSCLC. Muscle dysfunction assessment covers lean body mass and a 6MWT. NSCLC patients that met the inclusion criteria from September–November 2020 count 49 subjects. There were 3 subjects discontinued the study post-treatment because of passed away and statistical analysis was carried out on 46 research subjects which 2 subjects from the first group and 1 subject from the third group.

The research subjects were 46 subjects with NSCLC consisting of 32.6% males and 67.4% females. These data are similar to several studies including studies by Zhang in the year 2016 stated that EGFR mutation is higher in a woman 43.7% compared to men 24%.[20] Average age of subjects in creatine monohydrate supplementation combined with upper limb exercise group was 60.7±7.43 years, the creatine monohydrate supplementation-only group was 58.1±8.16 and in the control group 53.1±14.17. A study by Devi in 2021 showed that NSCLC patients at dr. Moewardi is mostly 60-70 years.[21]

There are 26.1% subjects who have a smoking history and 73.9% subjects have no smoking history. Other criteria with exon 19 mutation happened in 69.6%. These data are similar to the study by Zhang (2016) which patients with NSCLC without a smoking history were 49.3% compared to those with no smoking history by 21.5%. Most of the research subjects with exon 19 mutations were 75.21%.[20]

The study by Hsu et al (2018) reported that EGFR mutations occur at some point between exons 18 and 21. Exon 19 deletions and mutations point L858R on exon 21 is a generally detected type mutation and accounted for 50% and 40% of all patients, respectively. The two types of mutations are sensitization mutations and tumors with these mutations are sensitive to EGFR tyrosine kinase inhibitors (TKI).[3]

The average value of initial lean body mass in the first group was 34.01±7.16 kg and 74.24±5.19 %, respectively. The average initial lean body mass in the second group was 32.23±6.33 kg and 72.15±8.76%, and in the third group was 36.53±9.55 kg and 69.17±8.11 %, respectively. The increasing of lean body mass in the first group of was 4.22±1.81 and 6.38±2.4 %, (P=0.0001) greater and statistically significant.

A study by Xiao et al in 2017, based on the National data Health and Nutrition Examination Survey (NHANES) III obtained the median value of percetage body fat is 24% in men and 40% in women aged less than 40 years with body mass index normal, as well as 28% for men and 45% for women aged >70 years. The normal value for lean body mass is 70–90% of total body weight.[22] Increasing of lean body mass on the first group and second group showed a normal value so that supplementation with creatine monohydrate can help improve lean body mass clinically assisted by a combination of upper limb exercise so that the addition of lean body mass increased.

The research data according to a study by Olsen in 2006 reported that in healthy humans, creatine monohydrate supplementation in combination with progressive resistance training (PRT) strengthened the increase in satellite myocytes and concentration of myonuclei in skeletal muscle fibers, thereby facilitating muscle growth and hypertrophy.[23] Other studies by Sakkas in 2009

demonstrated that creatine monohydrate supplementation augmented the effects of PRT on muscle strength, energy, and body composition in 27 immunocompromised patients.[24]

Studies related to supplementation of creatine monohydrate by Jatoi (2017) failed to show the benefit which can be demonstrated in lean body mass, muscle strength or function. Inactive muscle conditions can cause decreased absorption of creatine monohydrate thereby interfering with the effects of creatine supplementation on lean body mass and muscle strength.[25]

The average of initial 6MWT in the first group obtained 225±72.39, 206±69.23 for second group, and in the third group was 223±76.69 (*P*=0.729) after the one-way ANOVA test showed no significant difference between groups. The average value of the 6MWT after treatment in the first group was 329±70.42, 268±65.31 for second group and 268±79.38 in third group (*P*=0.033) after one-way ANOVA test showed there was difference mean among groups. The difference in the addition of a 6MWT in the first, second, and third group each 104±20.07, 62±28.69, and 45±19.89 respectively with each group conducted paired t-test and obtained *P*=0.0001 indicates there is a significant change.

The measurement of the 6MWT was carried out by the recommendations of the American thoracic society in 2002 as a measure of response to therapeutic interventions for cardiorespiratory disease.[9] The research data is similar to a study by Peddle-McIntyre in 2019 stated that patients who exercised a 6MWT were 63 meters higher than 122 meters.[6] Another study by Edbrooke 2019 showed a change in the 6MWT after the first 8 weeks of the intervention there was a difference between the control and intervention groups of 48 m.[19]

The average value of initial quality of life in the first group was 86±20.7, 85±20.9 for second group and in the third group was 96±14.6. all three groups showed no significant difference *P*=0.199. The average quality of life after treatment in the first group of was 107±15.89, in the second group was 96±20.32 and in the third group was 104±14.58 (*P*=0.2).

The different quality of life in were 20.8±10.75; 10.62±7.30; and 7.26±4.81 (*P*=0.0001) each group respectively. The data was similar to a study by Peddle-McIntyre in 2019 that reported that exercise in advanced lung cancer patients increased health-related quality of life (HRQoL) by 13.0 (*P*=0.005).[6] Another study by Gerritsen in 2016 reported that exercise intervention improved the quality of life in cancer patients significantly by 5.55 (SD=3.19-7.90) with *P*<0.001.[26]

Research data in the form of changes in lean body mass, 6MWT, and quality of life in the combination group of creatine monohydrate supplementation and upper limb exercise as first group, creatine monohydrate supplementation-only as second group, and the third group were tested for normality with the Kolmogorov-Smirnov test, and obtained lean data body mass and 6MWT distributed normally each value of *P*=0.2 and *P*=0.071 while the quality of life was not normally distributed (*P*=0.0001). The homogeneity test showed that the lean body mass and 6-minute walk test data were homogeneous with value of *P*=0.084 and *P*=0.173, respectively. Quality of life data in the study showed that the data was not homogeneous with value of *P*=0.001. Homogeneity test affected post hoc test after one-way test ANOVA.[24,25]

The study of Roger Harris (1992) showed that oral creatine intake can increase intramuscular creatine content to increase exercise capacity.[16] Study by Buford (2007) reported that creatine as supplement nutrition is most effective to increase exercise tolerance, muscle strength, and LBM.[27] Study by Greenhalf (1995) reported that consumption of creatine 20 grams/day for 5 days can increase more than 20% of muscle creatine in the form of PCr.17 Study by Hultman (1996) used tissue biopsy to determine total muscle creatine levels show that there was a decrease in total creatine levels of 6 mmol/kg dm at 14 days after creatine monohydrate supplementation was discontinued.[28]

Cr supplementation in patients with muscle inactivation did not show the expected effect. Olsen

(2006) reported that in healthy people, Cr supplementation in combination with progressive resistance training (PRT) strengthened the increasing number of satellite cells and concentration of myonuclei in skeletal muscle fibers, thereby facilitating muscle growth and hypertrophy.[23] Creatine monohydrate has also been shown to increase the expression of myogenin and other myogenic regulatory factors that regulate the expression of the myosin heavy chain, which affects the content of contractile proteins like actin and myosin.[13,14,29]

Lean body mass, 6-minute walk test, and quality of life of research subjects showed significant numbers after the one-way ANOVA test with value of *P*=0.0001 at that three variables. Post hoc test on the lean body mass and 6-minute walk test data using Bonferroni. The results of the Bonferroni test on lean body mass data showed significantly different results between the combination group of creatine monohydrate supplementation with upper limb exercise, compared to the creatine monohydrate supplementation-only group (*P*=0.005) and the control group (*P*=0.0001). There was no significant difference between the creatine monohydrate supplementation-only group with the control group (*P*=0.364).[24,25]

Bonferroni test results on 6-minute walk test data obtained different means between a combination of creatine monohydrate supplementation with upper limb exercise group, compared to the creatine monohydrate supplementation-only group (*P*=0.0001) and the control group (*P*=0.0001). There was no significant difference between the creatine monohydrate supplementation group and the control group (*P*=0.185).[24,25]

Post hoc test on the quality of life data used the Games-Howell test and obtained significantly different results among the combination of creatine monohydrate supplementation with the upper limb exercise group, compared with the creatine monohydrate supplementation-only group (*P*=0.014) and with the control group (*P*=0.001). There was no significant difference between the creatine monohydrate supplementation group and the control group (*P*=0.298). The results were consistent with a study by Sakkas (2009) showed that supplementation of creatine monohydrate augmented the effects of PRT on muscle strength, energy, and body composition in 27 immunocompromised patients, and the Jatoi study (2017) that supplementation with creatine monohydrate only failed to show any demonstrable benefit in lean body mass, strength or muscle function.[24,25]

LIMITATIONS

A limitation of this study is the possibility of data bias. Treatment in the form of supplementation and home-based exercise requires cooperation with the patient's family and regular monitoring. The patient's family cannot always be contacted for telemedicine. The assessment of the 6-minutes walking test criteria after treatment was influenced by the results of the initial assessment.

CONCLUSION

Creatine monohydrate supplementation and upper limb exercise affect the lean body mass, 6-minute walk test, and quality of life in NSCLC patients. A combination of creatine monohydrate supplementation and upper limb exercise has superior effects compared to creatine monohydrate only and control.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. Ann Glob Heal.

2019;85:1–16.

2. Hung R, Krebs P, Coups EJ, Feinstein MB, Park BJ, Burkhalter J, et al. Fatigue and functional impairment in early-stage non-small cell lung cancer survivors. J Pain Symptom Manage. 2011;41:426–35
3. Hsu WH, Yang JCH, Mok TS, Loong HH. Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol. 2018;29:i3–9.
4. Henke CC, Cabri J, Fricke L, Pankow W, Kandilakis G, Feyer PC, et al. Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. Support Care Cancer. 2014;22:95–101.
5. Wang H, Liu X, Rice SJ, Belani CP. Pulmonary rehabilitation in lung cancer. PM R. 2016;8:990–6
6. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for advanced lung cancer. Cochrane Rev. 2019;2:CD012685.
7. Zeng Y, Jiang F, Chen Y, Chen P, Cai S. Exercise assessments and trainings of pulmonary rehabilitation in COPD: A literature review. Int J Chronic Obstr Pulm Dis. 2018;13:2013–23.
8. Gea J, Casadevall C, Pascual S, Orozco-Levi M, Barreiro E. Respiratory diseases and muscle dysfunction. Expert Rev Respir Med. 2012;6:75–90.
9. American Thoracic Society Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. American Thoracic Society statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7
10. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American thoracic society/european respiratory society statement on pulmonary rehabilitation. Am J Respir Crit Care Med. 2006;173:1390–413.
11. Yu S, Visvanathan T, Field J, Ward LC, Chapman I, Adams R, et al. Lean body mass: the development and validation of prediction equations in healthy adults. BMC Pharmacol Toxicol. 2013;14:1–9.
12. Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. Clin Pharmacokinet. 2003;42:557–74.
13. Gualano B, Artioli GG, Poortmans JR, Lancha Junior AH. Exploring the therapeutic role of creatine supplementation. Amino Acids. 2010;38:31–44.
14. Gualano B, Roschel H, Lancha AH, Brightbill CE, Rawson ES. In sickness and in health: The widespread application of creatine supplementation. Amino Acids. 2012;43:519–29.
15. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev. 2000;80:1107–213.
16. Hespel P, Eijnde BO, Derave W, Richter EA. Creatine supplementation: exploring the role of the creatine kinase/phosphocreatine system in human muscle. Can J Appl Physiol. 2001;26 Suppl:S79-102.
17. Armstrong M, Vogiatzis I. Personalized exercise training in chronic lung diseases. Respirology. 2019;24:854–62.
18. Cavalheri V, Granger CL. Exercise training as part of lung cancer therapy. Respirology. 2020;25:80–7.
19. Edbrooke L, Aranda S, Granger CL, Mcdonald CF, Krishnasamy M, Mileshkin L, et al. Multidisciplinary home-based rehabilitation in inoperable lung cancer: a randomised controlled trial. Thorax. 2019;74:787–96.
20. Zhang Y, Yuan J, Wang K, Fu X. The prevalence of EGFR mutation in patients with non-small cell lung cancer : a systematic review and meta-analysis. Oncotarget 2016;7:9–13.

21. Hapsari BDA. Perbandingan efikasi afatinib dan erlotinib sebagai terapi lini pertama kanker paru jenis adenokarsinoma dengan mutasi EGFR. Universitas Sebelas Maret; 2021.
22. Xiao J, Purcell SA, Prado CM, Gonzalez MC. Fat mass to fat-free mass ratio reference values from NHANES III using bioelectrical impedance analysis. Clin Nutr. 2018; 37: 2284–7
23. Olsen S, Aagaard P, Kadi F, Tufekovic G, Verney J, Olesen JL, et al. Creatine supplementation augments the increase in satellite cell and myonuclei number in human skeletal muscle induced by strength training. J Physiol. 2006;573:525–34.
24. Sakkas GK, Mulligan K, Dasilva M, Doyle JW, Khatami H, Schleich T, et al. Creatine fails to augment the benefits from resistance training in patients with HIV infection: a randomized, double-blind, placebo-controlled study. PLoS One. 2009;4:e4605.
25. Jatoi A, Steen PD, Atherton PJ, Moore DF, Rowland KM, Le-Lindqwister NA, et al. A double-blind, placebo-controlled randomized trial of creatine for the cancer anorexia/weight loss syndrome (N02C4): an alliance trial. Ann Oncol. 2017;28:1957–63.
26. Gerritsen JKW, Vincent AJPE. Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2016;50:796–803.
27. Fairman CM, Kendall KL, Hart NH, Taaffe DR, Galvão DA, Newton RU. The potential therapeutic effects of creatine supplementation on body composition and muscle function in cancer. Crit Rev Oncol Hematol. 2019;133:46–57
28. Hultman E, Söderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. J Appl Physiol. 1996;81:232–7.
29. Deacon SJ, Vincent EE, Singh SJ, Steiner MC, Greenhaff P, Morgan MD, et al. Does creatine supplementation enhance the effects of physical training during pulmonary rehabilitation in COPD? Eur Respir Rev. 2006;15:187–9

Original Article

Association between Obesity and COVID-19 Outcomes in the Intensive Care Unit of RSUP Dr. M. Djamil Padang

Ilham, Fenty Anggrainy, Dessy Mizarti

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

Abstract

Background: Obesity is one of the risk factors for severe clinical COVID-19. This is because these patients tend to have comorbidities such as metabolic disease and cardiovascular disease. Obesity may result in poor outcomes, such as prolonged hospital stays, higher incidence of ARDS and mortality. The purpose of this study was to determine the correlation between obesity and the outcome of confirmed COVID-19 patients.

Methods: This was an analytical study with retrospective cohort design on COVID-19 patients treated in the intensive care unit (ICU) of RSUP Dr. M. Djamil Padang. Data were taken from patients' medical records between November 2021 and February 2022. The correlation between obesity with length of stay and patient mortality was analyzed using Chi-square test. Odds ratio was also assessed.

Results: This study obtained that the characteristics of obese COVID-19 patients were mainly women (54.20%). The most dominant age group was 60-69 years (31.3%). About83.3% of obese patients were found to be clinically critical. Inflammatory markers such as procalcitonin, ferritin, IL-6 and d-dimer were not significantly associated with obesity. Diabetes mellitus was significantly related to the outcome of COVID-19 patients with obesity and without obesity (0.009%). Obesity was not correlated with hospital length of stay of COVID-19 patients but was significantly associated with length of stay in the ICU [OR=3.67 (95% CI=1.09-12.35)]. Obesity was significantly associated with mortality [OR=2.84 (95% CI=1.12-7.18)] and length of conversion for COVID-19 patients in the ICU [OR=30.00 (95% CI=2.85-31, 61)]. The expansion of adipose tissue both subcutaneously and viscerally which could be observed in obese patients can increase the proinflammatory, prothrombotic, and vasoconstrictive state that might affect the clinical deterioration of COVID-19 patients. This condition also manifests as insulin resistance, hypertension, atherosclerosis, cardiovascular disease and immunocompromised conditions which can generate high mortality rate.

Conclusion: Obesity was found to be significantly associated with mortality, conversion time and length of stay for COVID-19 patients in the ICU.

Keywords: COVID-19, obesity, length of stay, length of conversion, mortality

Corresponding Author:
Ilham | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, RSUP Dr. M Djamil Padang, Indonesia | ilh_am200@hotmail.com

Submitted: June 6th, 2022
Accepted: September 26th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 268–76
https://doi.org/10.36497/jri.v42i4.363

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a new type of coronavirus, first discovered on December 8, 2019 in Wuhan, China where several cases of clinical symptoms could progress to acute respiratory distress syndrome and death. The COVID-19 pandemic has spread throughout the world and various studies are being conducted to identify groups that are vulnerable of developing severe and life-threatening symptoms.[1]

Several studies were conducted to identify the effects of obesity and poor outcomes of COVID-19 patients. Williamson, et al. reported that obesity was one of the risk factors for severe clinical COVID-19, this was due to comorbidities such as metabolic disease and cardiovascular disease.[2] Albashir, et al. reported that 85% of obese patients required mechanical ventilation.[3] Rao, et al. also reported that being overweight was an independent risk factor for the severity of COVID-19.[4]

ObeseCOVID-19 patients had higher mortality rate, longer duration of hospitalization, greater incidence of ARDS and more frequent intensive care needs compared to patients with normal weight.[5–9] The high risk of obeseCOVID-19 patients for experiencing severe and critical clinical conditions that requires intensive care and the occurrence of poor outcomes, makes it important to determine the relationship between obesity and the outcomes of COVID-19 patients.

METHODS

An analytic retrospective cohort study was conducted from November 2021 to February 2022 at RSUP Dr. M. Djamil Padang. The study population was all confirmed COVID-19 patients who were treated in the intensive care unit (ICU) of RSUP Dr. M. Djamil Padang between January and August 2021. The inclusion criteria were confirmed COVID-19 patients from the results of SARS-CoV-2RT-PCR taken from a nasal/nasopharyngeal swab, aged >18 years, complete data of recent weight and height in the medical records. Exclusion criteria were COVID-19 patients with pregnancy, ascites and/or edema, or patients who were discharged with at their own will (against medical advice).

The characteristic data were presented in the form of a frequency distribution table. The analysis was carried out using the SPSS version 21 program. The correlation between demographic characteristics, clinical degrees, inflammatory markers and comorbidities of COVID-19 patients were analyzed using the Chi-square test on categorical variables while the numerical variables were analyzed using the Independent Sample T test. The association between obesity, length of stay and mortality was analyzed using Chi-square test and the odds ratio was assessed in each category (OR>1, is risk factor, when OR<1, is protective factor, and OR=1, is not a risk factor & not a protective factor).

RESULTS

The number of samples that met the research requirements were 96 patients. Characteristics of COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang is described in Table 1. This study obtained that most obese patients were in the age group of 60–69 years (31.3%) with more than half of them were women (54.2%), while the non-obese patients were mostly male (66.7%) in the age group of 60-69 years (33.3%). Most critical clinical cases were observed in both group of obese (83.3%) and non-obese patients (89.6%). The results of inflammatory markers such as procalcitonin, IL-6, D-dimer and ferritin, had median values that were almost the same in both obese and non-obese groups. Diabetes mellitus was the most common comorbid disease in the obese group (45.8%), while in the non-obese group it was hypertension (35.4%). There were more obese patients who had >1 comorbidities than the non-obese group (27.1% vs 14.6%).

Table 1 points out that there were no differences related to age (*P*=0,76), gender (*P*=0.064), clinical severity (*P*=551) and inflammatory markers between groups of obese and non-obese COVID-19 patients. The results revealed that there was no difference in the number of patients with one comorbidity between the obese and non-obese groups. Patients who had >1 comorbidities were found to be more on obese than non-obese patients, but from the results were not statistically significant. The most common comorbidities obtained in obese COVID-19 patients were diabetes mellitus (45.8%), hypertension (33.33%), and chronic kidney disease (16.7%). The length of hospital stay was shorter in obese patients compared to non-obese. The difference between obese and non-obese COVID-19 patients with comorbidities was found to be significant in patients with diabetes mellitus (*P*=0.009).

This study reported a total of 96 patients were admitted to the ICU, 68 of whom died and no PCR swab examination was performed, so that only 28 survived patients underwent PCR swab conversion which was then assessed for its association with obesity. The relationship between obesity and PCR conversion time in the ICU can be seen in Table 2.

Table 2 indicates that patients with length of stay in the ICU <14 days were found more in obese group (75.0%) compared to non-obese group (25.0%). Based on analysis using the Chi-square test, it was known that there was a relationship between obesity and the length of stay for COVID-19 patients in the ICU (*P*<0.05), with OR=3.67 (95% CI=1.09–12.35).

Table 3 shows that COVID-19 patients who died in the ICU were found more in obese patients (57.4%) compared to non-obese patients (42.6%). Based on the analysis using Chi-square test, there was a relationship between obesity and mortality of COVID-19 patients in the ICU (*P*<0.05), with OR=2.84 (95% CI=1.12–7.18).

Table 1. Characteristics of confirmed COVID-19 patients with and without obesity in the ICU of RSUP Dr. M. Djamil Padang

Patient Characteristics	Obese (n=48)	Non-obese (n=48)	*P*
Age group, f (%)			
<50 years	11 (22.90%)	8 (16.70%)	0.706[a]
50–59 years	13 (27.10%)	11 (22.90%)	
60–69 years	15 (31.30%)	16 (33.30%)	
≥70 years	9 (18.80%)	13 (27.10%)	
Gender			
Men	22 (45.80%)	32 (66.70%)	0.064[a]
Women	26 (54.20%)	16 (33.30%)	
Clinical severity, f (%)			
Severe	8 (16.70%)	5 (10.40%)	0.551[a]
Critical	40 (83.33%)	43 (89.60%)	0.551[a]
Inflammation markers, median (min-max)			
Procalcitonin (ng/ml)	0.75 (0.05–171.00)	0.28 (0.05–171.42)	0.114[b]
IL-6 (pg/ml)	73.70 (1.70–1,482.00)	42.35 (1.50–902.80)	0.570[b]
Ferritin (µg/L)	1,107.58 (11.30–12,001.00)	1,201.00 (11.30–12,001.00)	0.235[b]
D-Dimer (ng/ml)	3,494.50 (587.00–71,901.00)	3,400.50 (216.00–10,001.00)	0.930[b]
Comorbidity, f (%)			
Hypertension	16 (33.33%)	17 (35.40%)	1.000[a]
Diabetes mellitus	22 (45.80%)	9 (18.80%)	0.009[a*]
Chronic liver disease	1 (2.10%)	0 (0.00%)	n/a
Malignancy	1 (2.10%)	1 (2.10%)	1.000[a]
Chronic lung disease	1 (2.10%)	2 (4.20%)	1.000[a]
Chronic kidney disease	8 (16.70%)	6 (12.50%)	0.772[a]
Immunodeficiency	0 (0.00%)	1 (2.10%)	n/a
Number of comorbidities, f (%)			
None	14 (29.20%)	20 (41.70%)	
1 comorbidity	21 (43.80%)	21 (43.80%)	0.239[a]
>1 comorbidities	13 (27.10%)	7 (14.60%)	
Length of stays in hospital (mean±SD)	10.58±6.99	12.35±9.62	0.305

Note=*P*<0,05 significant; n/a not account; [a]Chi-square test; [b]Mann-whitney test

Table 2. The correlation between obesity and length of stay for COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang (n=96)

Obesity	Length of stay		Total	*P*	OR (95% CI)
	≥14 days	<14 days			
Obese	12 (75.0%)	36 (45.0%)	48 (50.0%)	0.045	3.67 (1.09–12.35)
Non-obese	4 (25.0%)	44 (55.0%)	48 (50.0%)		

Table 3. The correlation between obesity and mortality of COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang (n=96)

Obesity	Mortality		Total	*P*	OR (95% CI)
	Died	Survive			
Obese	39 (57.4%)	9 (32.1%)	48 (50.0%)	0.043	2.84 (1.12–7.18)
Non-obese	29 (42.6%)	19 (67.9%)	48 (50.0%)		

Table 5. The correlation between obesity and PCR conversion time of COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang (n=96)

Obesity	Conversion length		Total	*P*	OR (95% CI)
	≥14 days	<14 days			
Obese	8 (88.9%)	1 (11.1%)	9 (42.9%)	0.001	30.00 (2.85–31.61)
Non-obese	4 (21.1%)	15 (78.9%)	16 (57.1%)		

Table 4 reveals that COVID-19 survivor with conversion time of ≥14 days were found more in obese patients (88.9%) than non-obese patients (11.1%). Based on the analysis using Chi-square test, there was a relationship between obesity and conversion time of COVID-19 patients in the ICU (*P*<0.05), with OR=30.00 (95% CI=2.85-31.61).

DISCUSSION

The characteristics of COVID-19 patients in the ICU who were obese were mostly in the 60–69 years age group, which was 31.3% of total obese patients, followed by the 50–59 years age group. Dana, et al. who conducted a study in France also observed that the age group in obese COVID-19 patients was mostly

60–75 years old.[10] A cohort study by Pettit, et al. in Chicago also reported that the median age of hospitalized overweight and obese COVID-19 patients ranged from 51.1 years to 63.4 years.[11]

Another study by Surendra in Jakarta on hospitalized COVID-19 patients revealed that the most common age groups were 50-59 years (22%) and 40–49 years (19%).[12] COVID-19 can develop at any age, but its incidence and severity increase with age. There are two factors which affect the severity of age-related COVID-19 cases, including the escalating number of comorbidities that elderly patients have and dysregulation of the immune system as people aged.[13]

Aging process is associated with a change in pathogen recognition and clearance due to a decrease in T-cells and accumulation of memory T-cells. The aging process increases the risk of inflammation and death due to an imbalance in immune system function. Patients aged 50 years and over have a higher expression of ACE2 which is encoded by the ACE2 gene with other factors such as decreased immunity, decreased organ function and comorbidities that can increase the risk of death. Older age also has an inefficient antiviral response due to imbalanced cytokine release.[14]

More than half of obese COVID-19 patients in this study were female (54.2%). Estrogen plays a role in increasing body fat mass with age, especially after adolescence. History of pregnancy and childbirth are also factors that increase the risk of women experiencing obesity.[15] This study also observed that there were more male patients in the non-obese group (66.7%). Surendra, et al. also reported that the prevalence of male patients hospitalized due to COVID-19 was higher than the female (92%).[12] Women are less susceptible to COVID-19 infection, this was related to innate immunity, steroid hormones and factors associated with sex chromosomes. Immune regulatory genes encoded by the X chromosome in women lead to lower viral load and decreased inflammation compared to men, in addition to higher CD4+ T-cells and a better immune response in women. TLR7 levels in women are also higher and biallelic expression indicates a better immune response and intensifies resistance to viral infections. Men are associated with poorer lifestyles such as smoking and higher alcohol consumption.[16]

Most of the obese COVID-19 patients had critical clinical degrees, which was 83.3% of all patients in the ICU, this is in line with study by Dana, et al. who reported that among 222 patients admitted to the COVID-19 ICU, only 15.3% had a BMI within normal limits, the remainder being patients with mild to severe obesity.[10] A meta-analysis by Zhang, et al. pointed out that obese patients had a higher risk of requiring hospitalization when infected with COVID-19 and experienced a more severe clinical course.[17]

Adipose tissue in obesity produces proinflammatory cytokines and hormones that can have direct effects on the lungs. These mediators are released from adipose and leukocytes that infiltrate adipose tissue. These inflammatory factors then enter the circulation, including leptin, TNF-α, IL-6 and IL-8,[10] C-reactive protein, and monocytes chemoattractant protein-1 (MCP-1). Chronic inflammation in obesity initially occurs in adipose tissue, but later this process progresses to systemic inflammation.[18]

There was a difference in the median values of inflammatory markers procalcitonin, IL-6 and D-dimer, which were higher in the obese group than non-obese, while the median value of ferritin was lower in the obese group than in the non-obese group, but the difference was not statistically significant. Ellulu, et al. in Malaysia stated that obesity predisposed to a pro-inflammatory state through the mechanism of increasing inflammatory mediators, namely IL-6 and TNF-α compared to non-obese populations. IL-6 levels are associated with obesity which can affect the liver to synthesize and secrete CRP.[19]

A study by Ferreira, et al. also observed increased CRP, ferritin and D-dimer values among obese patients. Obesity induces chronic inflammation, so that IL-6 and TNF-α values are consistently elevated in the circulation in both human and mouse models. This increase induces an inflammatory state through elevated infiltration of macrophages into adipose tissue, macrophage polarization and augmentation of cytokines and chemokines.[20]

About 43% of obese COVID-19 patients had one comorbidity and 27.1% of them had more than one comorbidity. COVID-19 patients with obesity are most often accompanied by diabetes mellitus, followed by hypertension and kidney disease. These results are similar to study by Ferreira, et al. who reported that the most common comorbidities accompanying obese patients were hypertension and diabetes mellitus.[20] Obesity is a risk factor for the occurrence of type 2 diabetes mellitus caused by impaired sensitivity of muscle and fat tissue to insulin resulting in insulin resistance.[21]

A study by Heialy, et al. in Dubai found that obese patients had more comorbidities such as cardiovascular disease, hypertension, diabetes mellitus, cancer, and chronic kidney disease (78%) compared to patients with normal BMI (40%).[22] COVID-19 patients with obesity and diabetes mellitus have immune dysregulation such as phagocytic cell dysfunction, impaired immune cell chemotaxis, impaired T cell response, and altered cytokine production, which leads to ineffective microbial clearance during viral infections and prolongs the duration of viral conversion. This situation escalates mortality by extending inflammatory state of the body. Obesity and diabetes separately increase poor outcomes in COVID 19 patients. This could be seen from the results of several studies which reported an increase in mortality, length of stay and the need for ICU as well as the duration of viral conversion. Therefore, the combination of these two conditions was expected to further worsening the outcome of COVID-19 patients.

The mean length of stay for obese COVID-19 patients in hospitals was shorter than the non-obese, although the results were not significant. There was no relationship between obesity and length of stay for COVID-19 patients. Pouwels, et al. in Netherlands stated similar results where there was no significant difference of the median duration of hospitalization on COVID-19 patients between the non-obese group and the obese group.[23] Dana, et al. also reported that there was no significant difference between the length of stay of patients with normal weight, overweight and obesity, both in recovered and deceased COVID-19 patients.[10] This might be due to the assessment of the length of stay in this study was not only for patients who were discharged as survivor but also for patients who were not survive during hospital stay. This study revealed that 70.8% of COVID-19 patients admitted to the COVID-19 ICU died, resulting in a high mortality rate that was biased towards the total length of stay in the hospital.

More obese COVID-19 patients died in the ICU (57.4%) than non-obese patients (42.6%). The results of statistical analysis showed that there was a relationship between obesity and mortality of COVID-19 patients in the ICU (P<0.05) with OR=2.84 (95% CI=1.12-7.18). Poly, et al. also stated that obesity was significantly associated with an increased risk of death among COVID-19 patients, especially in patients over 65 years of age.[24] The underlying mechanisms involve abnormalities in the balance of leptin and adiponectin, increased ACE-2 expression, altered pulmonary physiology and impaired lung function that may promote the development of respiratory viral infections in obese patients.[25]

Tartof, et al. also reported that there was an association between BMI and risk of death, even after adjustment for obesity-related comorbidities.[26] Obesity is associated with chronic hypertension through increased heart rate, cardiac output and renal tubular sodium reabsorption as well as impaired renal natriuresis pressure, which occurs as a direct result of α-adrenergic and β-adrenergic receptors stimulations and indirectly through activation of other systems such as RAAS and sympathetic nervous system.[27] Obesity has a substantial effect on the immune system, where adipocytes are able to produce mediators such as cytokines, chemokines and adipokines that lead to chronic inflammation, cell necrosis as well as cell dysfunction and at a systemic level alter the immune response. In addition, the leptin resistance observed in obesity also causes an immunosuppressive phenotype.[28]

Severe obesity, particularly among younger patients, and the risk of death posed by other obesity-related comorbidities, such as history of myocardial infarction, diabetes, hypertension, or hyperlipidemia,

suggest a significant pathophysiological relationship between excess adiposity and COVID-19 with a clinically significant degree of obesity. Obesity is not only an extension of subcutaneous adipose tissue but is also associated with an increase in ectopic fat, including visceral, perivascular, and epicardial adipose tissue. This fat distribution promotes chronic proinflammatory, prothrombotic, and vasoconstrictive states, which can manifest as insulin resistance, type 2 diabetes, hypertension, atherosclerosis, cardiovascular disease and immunocompromised states leading to high mortality rates. In addition to chronic disease, visceral adiposity also increases mortality among critically ill patients with ARDS.[29]

COVID-19 survivor who had a conversion time of ≥14 days were found to be more in obese patients (88.9%) than non-obese patients (11.1%). The difference was significant with *P*<0.05 and OR=30.00 (95%=CI 2.85-31.61). A cohort study by Bennasrallah, et al. in Tunisia obtained that the median conversion time for COVID-19 patients was 20 days (IQR=17-32 days). This study observed that the presence of symptoms and the use of masks were associated with conversion time, whereas increase in age, gender, comorbidities and smoking habits were not associated with an escalated conversion time.[30]

Mo, et al. in Wuhan stated that most of obese patients had mean conversion time of 18 days (IQR=11-25 days) starting from the first day of symptoms onset, with factors related to the prolongation of conversion time was cough, high levels of leukocytes, neutrophils and ESR as well as low values of CD3+ and CD4+ lymphocytes.[31] This difference might be associated to the heterogeneity of the patients and the severity of disease in this study. Study by Zhang, et al. in China comparing COVID-19 patients with obesity and non-obesity revealed that on day 14, about 94.9% of non-obese patients had converted.[32] This study suggested that obesity status was a positive risk factor for viral clearance at day 14. Another study by Moriconi, et al. also reported a longer conversion time in obese patients than non-obese patients (19±8 vs 13±7 days, *P*=0.002).[7]

Obesity is often accompanied by insulin and leptin resistance which interfere with viral clearance. ACE2 produced by adipocytes which provide viral enter the adipose tissue, therefore adipose tissue had their role as a reservoir place of virus. The expanded of adipose tissue could lead to the oxidative stress in cells, after which increase viral receptor expression in adipose tissue and other organs. Obese patients with diabetes experience dysregulation of immune deposition such as phagocytic cell dysfunction, impaired neutrophil movement, impaired T cell-mediated immune response, altered cytokine production, leading to interrupt and ineffective microbial clearance during viral infections.[33,34]

The length of stay for ≥14 days in the ICU was observed more in obese patients (75.0%) than in non-obese patients (25.0%) with the results showing that there was a correlation between obesity and the length of stay for COVID-19 patients in the ICU with *P*<0.05 and OR=3.67 (95% CI=1.09-12.35). A study by Sjogren, et al. in Sweden reported that obese individuals had longer duration of hospitalization and BMI was one of the determinants of prolonged hospitalization in COVID-19 patients. An increase of one standard deviation of BMI was associated with 1.35 days longer intensive care (95% CI=0.58-2.11) in linear regression after adjusting for age, sex and comorbidities. A longer length of stay reflects a more severe disease course and is associated with greater functional impairment in COVID-19 patients.[35]

Moriconi, et al. revealed that obese patients required mechanical ventilation and longer hospital stay (21±8 vs 13±8 days, *P*=0.0008).[7] Another study by Suresh, et al. and Plataki, et al. obtained different results in which obesity was found to be unrelated to the need for mechanical ventilation needs.[36,37] The mechanisms which influence the severity and the relationship to length of hospitalization may be multifactorial, ranging from decreased cardiorespiratory reserve and thrombogenesis, to hyperimmune reactivity. Expression of ACE2, the functional SARS-CoV-2 receptor and dysregulation of obesity in obese patients are some of the factors that can transform adipose tissue into a potential viral reservoir, as well as the effects of impaired cytokine balance. Regardless of the underlying mechanism,

there is a strong evidence that obese individuals are more likely to develop severe illness from COVID-19.[36]

LIMITATION

This study was conducted on patients with severe and critical clinical conditions in the ICU so that the patients already had poor outcomes from the time they were admitted to the hospital. As the only comorbidity that was statistically significant to the outcome of COVID-19 patients in this study, diabetes mellitus could be a confounding factor in determining the correlation between obesity status and length of hospitalization and mortality, therefore, further research is needed.

CONCLUSION

Characteristics of obese COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang were mostly woman aged 60-69 years. Diabetes mellitus was significantly associated with both obese and non-obese COVID-19 patients. Obesity was not associated with overall length of stay in the hospital. Obesity was found to be significantly correlated with mortality, conversion time and length of hospitalization for COVID-19 patients in the ICU.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. World Health Organization. Clinical management of COVID-19: Living guideline, 23 June 2022. 4th ed. Geneva: World Health Organization; 2022. 11–12 p.
2. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430–6.
3. Albashir AAD. The potential impacts of obesity on COVID-19. Clin Med. 2020;20(4):e109–13.
4. Rao X, Wu C, Wang S, Tong S, Wang G, Wu G, et al. The importance of overweight in COVID-19: A retrospective analysis in a single center of Wuhan, China. Medicine (Baltimore). 2020;99(43):e22766.
5. Bello-Chavolla OY, Bahena-López JP, Antonio-Villa NE, Vargas-Vázquez A, González-Díaz A, Márquez-Salinas A, et al. Predicting mortality due to SARS-CoV-2: A mechanistic score relating obesity and diabetes to COVID-19 outcomes in mexico. J Clin Endocrinol Metab. 2020;105(8):dgaa346.
6. Yu W, Rohli KE, Yang S, Jia P. Impact of obesity on COVID-19 patients. J Diabetes Complications. 2021;35(3):107817.
7. Moriconi D, Masi S, Rebelos E, Virdis A, Manca ML, De Marco S, et al. Obesity prolongs the hospital stay in patients affected by COVID-19, and may impact on SARS-COV-2 shedding. Obes Res Clin Pract. 2020;14(3):205–9.
8. Dreher M, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, et al. The characteristics of 50 hospitalized COVID-19 patients with and without ARDS. Dtsch Arztebl Int. 2020;117(16):271–8.
9. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med. 2020;180(11):1436–47.
10. Dana R, Bannay A, Bourst P, Ziegler C, Losser M-R, Gibot S, et al. Obesity and mortality in critically ill COVID-19 patients with respiratory failure. Int J Obes (Lond). 2021;45(9):2028–37.
11. Pettit NN, MacKenzie EL, Ridgway JP, Pursell K, Ash D, Patel B, et al. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. Obesity (Silver Spring). 2020;28(10):1806–10.

12. 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 Heal - West Pacific. 2021;9:100108.
13. Huang Y, Lu Y, Huang Y-M, Wang M, Ling W, Sui Y, et al. Obesity in patients with COVID-19: a systematic review and meta-analysis. Metabolism. 2020;113:154378.
14. Shahid Z, Kalayanamitra R, McClafferty B, Kepko D, Ramgobin D, Patel R, et al. COVID-19 and older adults: What we know. J Am Geriatr Soc. 2020;68(5):926–9.
15. Aslan G, Arli SK, Bakan AB. Obesity and risk factors in women aged between 18 and 64. Int J Caring Sci. 2019;12(1):218–23.
16. Bwire GM. Coronavirus: Why men are more vulnerable to COVID-19 than women? SN Compr Clin Med. 2020;2(7):874–6.
17. Zhang H, Han H, He T, Labbe KE, Hernandez A V, Chen H, et al. Clinical characteristics and outcomes of COVID-19-infected cancer patients: A systematic review and meta-analysis. J Natl Cancer Inst. 2021;113(4):371–80.
18. Cai Z, Yang Y, Zhang J. Obesity is associated with severe disease and mortality in patients with coronavirus disease 2019 (COVID-19): a meta-analysis. BMC Public Health. 2021;21(1):1505.
19. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017;13(4):851–63.
20. Rosário Ferreira ME, Santos de Andrade AV, Ferreira Queiroz AA, Martins-Filho PR, de Aquino Neves EL, Oliveira de Carvalho F, et al. COVID-19 and obesity: a systematic review and meta-analysis on the pre-existing clinical conditions, COVID-19 symptoms, laboratory findings and clinical outcomes. EXCLI J. 2021;20:1610–4.
21. Parmar M. Obesity and Type 2 diabetes mellitus. Integr Obes Diabetes. 2018;4.
22. Al Heialy S, Hachim MY, Hachim IY, Bin Naeem K, Hannawi H, Lakshmanan J, et al. Combination of obesity and co-morbidities leads to unfavorable outcomes in COVID-19 patients. Saudi J Biol Sci. 2021;28(2):1445–50.
23. Pouwels S, Ramnarain D, Aupers E, Rutjes-Weurding L, van Oers J. Obesity May Not Be Associated with 28-Day Mortality, Duration of Invasive Mechanical Ventilation and Length of Intensive Care Unit and Hospital Stay in Critically Ill Patients with Severe Acute Respiratory Syndrome Coronavirus-2: A Retrospective Cohort St. Med. 2021;57(7):674.
24. Poly TN, Islam MM, Yang HC, Lin MC, Jian W-S, Hsu M-H, et al. Obesity and mortality among patients diagnosed with COVID-19: A systematic review and meta-analysis. Front Med. 2021;8:620044.
25. Osibogun A, Balogun M, Abayomi A, Idris J, Kuyinu Y, Odukoya O, et al. Outcomes of COVID-19 patients with comorbidities in southwest Nigeria. PLoS One. 2021;16(3):e0248281.
26. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. Ann Intern Med. 2020;173(10):773–81.
27. Shariq OA, McKenzie TJ. Obesity-related hypertension: a review of pathophysiology, management, and the role of metabolic surgery. Gland Surg. 2020;9(1):80–93.
28. Pugliese G, Liccardi A, Graziadio C, Barrea L, Muscogiuri G, Colao A. Obesity and infectious diseases: pathophysiology and epidemiology of a double pandemic condition. Int J Obes (Lond). 2022;46(3):449–65.
29. Ni Y-N, Yu H, Xu H, Li W-J, Liang B-M, Yang L, et al. High visceral adipose tissue to subcutaneous adipose tissue ratio as a predictor of mortality in acute respiratory distress syndrome. Am J Med Sci. 2019;357(3):213–22.
30. 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. Int J Infect Dis. 2021;105:463–9.

31. Mo P, Deng L, Liu X, Gao S, Liang K, Luo M, et al. Risk factors for delayed negative conversion of SARS-CoV-2 in patients with COVID-19 pneumonia: a retrospective cohort study. Epidemiol Infect. 2020;148:e293.
32. Zhang X, Lin B, Yang G, Liu L, Lu J, Lu Z, et al. Delayed SARS-CoV-2 clearance in patients with obesity. Infect Drug Resist. 2021;14:2823–7.
33. Demeulemeester F, de Punder K, van Heijningen M, van Doesburg F. Obesity as a Risk Factor for Severe COVID-19 and Complications: A Review. Cells. 2021;10(4):933.
34. Angelidi AM, Belanger MJ, Mantzoros CS. Commentary: COVID-19 and diabetes mellitus: What we know, how our patients should be treated now, and what should happen next. Metabolism. 2020;107:154245.
35. Sjögren L, Stenberg E, Thuccani M, Martikainen J, Rylander C, Wallenius V, et al. Impact of obesity on intensive care outcomes in patients with COVID-19 in Sweden-A cohort study. PLoS One. 2021;16(10):e0257891.
36. Suresh S, Siddiqui M, Abu Ghanimeh M, Jou J, Simmer S, Mendiratta V, et al. Association of obesity with illness severity in hospitalized patients with COVID-19: A retrospective cohort study. Obes Res Clin Pract. 2021;15(2):172–6.
37. Plataki M, Pan D, Goyal P, Hoffman K, Choi JMK, Huang H, et al. Association of body mass index with morbidity in patients hospitalised with COVID-19. BMJ open Respir Res. 2021;8(1).

Original Article

The Effect of Long-Acting Beta-2 Agonist Monotherapy and Long-Acting Anticholinergic Monotherapy to Quality-of-Life in Group B Stable COPD Patients

Tri Setia Negara Sinulingga,[1] Pandiaman Pandia,[1] Amira P. Tarigan,[1] Putri Chariani Eyanoer[2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara/ RSUP H. Adam Malik, Medan, Indonesia
[2]Department of Community Medicine, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

Abstract

Background: Based on the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD), treatment for group B stable COPD patients is a long-acting beta-2 agonist (LABA) or long-acting anticholinergic (LAMA). Some studies experienced that LAMA was better than LABA but the opposite was also found in several studies. COPD patients often experience a decline in physical activity which causes a decrease in quality of life. We aimed to compare the effect of LABA or LAMA on quality of life in group B stable COPD patients.

Methods: This was a study with case series design conducted on 50 COPD patients divided into two groups. The first group consisted of patients who used LABA for at least 3 months. The second group used LAMA for at least 3 months. All subjects filled in the SGRQ. The calculation of SGRQ was carried out using Microsoft Excel Calculator SGRQ.

Results: A total 41 men and 9 women were enrolled in this study. There was no significant difference between the use of indacaterol monotherapy and tiotropium monotherapy on the quality of life although tiotropium showed a better quality of life (76%) than indacaterol monotherapy (64%).

Conclusion: There was no significant difference in the use of indacaterol and tiotropium on the quality of life although in this case tiotropium showed better results (*P*=0.538).

Keywords: COPD, indacaterol, tiotropium, quality of life, SGRQ

Corresponding Author:
Tri Setia Negara Sinulingga | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, RSUP H. Adam Malik, Medan, Indonesia | trisinulingga@yahoo.com

Submitted: January 20th, 2020
Accepted: September 26th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 277–281
https://doi.org/10.36497/jri.v42i4.370

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one among a group of non-communicable diseases that is a public health problem in Indonesia. This is due to the increase in life expectancy and the higher exposure to risk factors, such as host factors that are thought to be associated with the incidence of COPD, the increasing number of smokers, especially in the younger age group, as well as indoor and outdoor air pollution and also pollution at work.[1]

Currently in Indonesia, COPD is estimated to have 4.8 million patients with a prevalence of around 5.6%. This figure will continue to increase along with the escalating number of smokers because 90% of COPD patients are smokers and ex-smokers.[2]

In 2011, COPD was listed as the third leading cause of death in the United States, and by 2030 it is estimated that the mortality rate of COPD will intensify to 4.5 million people annually.[3] The World Health Organization (WHO) states that by 2030, COPD will be the third leading cause of death in the world.[4]

Shortness of breath causes the patient to be panic, anxious and frustrated, so the patient reduces activity to avoid the difficulty in breathing. Patients will fall into physical deconditioning, which is an adverse condition due to low activity that could affect the musculoskeletal, respiratory, cardiovascular and other systems. This situation causes a decline in functional capacity, so that the quality of life also decreases.[5] One of the measuring tools used to evaluate the quality of life of COPD patients is the Saint George's Respiratory Questionnaire (SGRQ).

In pharmacological therapy, the drugs most often used for COPD patients are bronchodilators with two types: beta-2 agonists and anticholinergic drugs.[6] Beta-2 agonists work by relaxing respiratory smooth muscle through stimulation of beta-2 adrenergic receptors that are abundant in airway smooth muscles. Stimulation of beta-2 adrenergic receptors at the cellular level will stimulate G protein to activate adenylate cyclase which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), resulting in decreased calcium release and changes in membrane potential that cause muscle relaxation. Intracellular cAMP plays a role in regulating respiratory smooth muscle tone, resulting in bronchodilation. In addition, beta-2 agonists, which also stimulate beta-2 adrenergic receptors in the presynaptic parasympathetic ganglia of the airways, inhibit the release of acetylcholine, which is a bronchoconstrictor, inducing bronchodilation.[7]

Anticholinergic or antimuscarinic bronchodilators are non-selective cholinergic muscarinic receptor antagonists that act by blocking parasympathetic acetylcholine. Acetylcholine binds to M1 and M3 and causes smooth muscle contraction via an increase in cyclic guanosine monophosphate (cGMP) or by activation of G protein. This protein then activates phospholipase C to produce inositol triphosphate (IP3), leading to the release of calcium from intracellular stores and activation of myosin light chain kinase which then causes smooth muscle to contract. Anticholinergics block this cascade and reduce smooth muscle tone by reducing intracellular calcium release.[8]

Based on 2019 GOLD, the treatment options for group B stable COPD were long-acting beta-2 agonists (LABA) or long-acting antimuscarinics (LAMA). Examples of LABA are indacaterol and salmeterol while the example of LAMA is tiotropium.[3] Data regarding the different effects of LABA or LAMA bronchodilators on quality of life in group B stable COPD patients in Indonesia are still very limited. With this background, we were interested in conducting a study on the effect of indacaterol monotherapy versus tiotropium monotherapy on quality of life in group B stable COPD patients.

METHODS

This was a descriptive study with a case series design from April 2019 to June 2019, at the outpatient clinic of H. Adam Malik Hospital Medan and the Education Hospital of Universitas Sumatra Utara, Medan.

All study subjects were group B stable COPD patients who had received indacaterol or tiotropium for at least the past 3 months. Patients were then interviewed and an informed consent was given for the study; then, the patients were asked to complete the SGRQ under the direction of the researcher. The SGRQ contains 50 questions, consisting of symptom domains on questions 1-8, activity domains on questions 11-17 and 36-44, and impact domains on questions 9,10, 18-35 and 45-50. The calculation of the score is a total processing of 50 statements where each alternative answer to the respondent on the SGRQ has a weight.[8] Furthermore, the total score is calculated using the standard Microsoft Excel "Calculator SGRQ" software.

The Health Research Ethics Committee approved the research procedure. Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS), where the value of $P<0.05$ was considered significant.

RESULTS

In this study, the majority of subjects were male, users of indacaterol (86%) and tiotropium (88%), mostly in age range of 60-69 years, where in this age range, users of indacaterol were 13 people (52%) and tiotropium were 11 people (44%). Most of the subjects were Batak ethnic with 14 indacaterol users (56%) and 17 tiotropium users (68%). All study subjects had a smoking history with severe Brinkman index, consisted of 21 indacaterol users (84%) and 14 tiotropium users (56%). Most subjects taking indacaterol and tiotropium were in the obesity criteria. The characteristics of the study subjects can be seen in Table 1.

Table 2 below indicates that the use of tiotropium monotherapy resulted in a better quality of life (76%) than indacaterol monotherapy (64%).

Table 1. Characteristics of Research Subjects

Characteristics	Indacaterol		Tiotropium	
	N	%	N	%
Age				
40–49 years	5	20.0	4	18.0
50–59 years	5	20.0	6	24.0
60–69 years	13	52.0	11	44.0
≥70 years	2	8.0	4	18.0
Gender				
Men	19	86.0	22	88.0
Women	6	24.0	3	12.0
Occupation				
Civil Servant	4	18.0	3	12.0
Retired	8	32.0	3	12.0
Farmer	5	20.0	4	18.0
Self-employed	8	32.0	15	60.0
Brinkman Index				
Mild	0	0	3	3.0
Medium	4	16.0	8	32.0
Severe	21	84.0	14	56.0
Ethnic group				
Bataknese	14	56.0	17	68.0
Javanese	6	24.0	4	18.0
Etc.	5	20.0	4	18.0
Body mass index				
Underweight	1	4.0	1	4.0
Normoweight	3	12.0	7	28.0
Overweight	10	40.0	8	32.0
Obese	11	44.0	9	36.0

Statistical tests using chi-square test revealed no significant difference between indacaterol and tiotropium (*P*>0.05). In this case, the tiotropium group showed a higher value. This pointed out that many factors affect the quality of life of COPD patients other than indacaterol and tiotropium treatment, such as age, gender, healthy lifestyle, etc.

Table 2. Overview of Research Subjects' Quality of Life

Quality of Life	Indacaterol		Tiotropium		*P*
	N	%	N	%	
Good	16	64.0	19	76.0	0.538*
Bad	9	36.0	6	24.0	
Total	25	100.0	25	100	

Note: *chi-square

Details per domain could not be displayed because the calculation of the SGRQ score was done with the Microsoft excel SGRQ calculator tool which exhibited the overall live score.

DISCUSSION

In this study, the majority of the subjects were male. This is in line with the actual conditions that we could observe: men are the most common patients with COPD. The high prevalence of COPD in males is related to the fact that the prevalence of smoking is 16 times higher in males (65.9%) than females (4.2%).[9]

The majority of subjects were aged 60-69 years where in this age group, 13 people (52%) were indacaterol users and 11 people (44%) were tiotropium users. This is identical to a study conducted at the H Adam Malik Hospital, which pointed out that the mean age of COPD patients was 61.4 years.[10] Age is associated with changes in lung structure and function that may intensify the pathogenesis of COPD, which can escalate the incidence of COPD in the elderly.[11]

Most subjects were Batak ethnic, where in this ethnicity, 14 people were indacaterol users (56%) and 17 were tiotropium users (68%). This is related to the culture of the Batak tribe, where cigarettes are used in several traditional events, and also the custom of the Batak tribe to smoke even from a young age.[12]

All study subjects had smoking history, and among these smokers with severe Brinkman index, 21 people used indacaterol (84%) and 14 used tiotropium (56%). This follows a related study in which most subjects had severe Brinkman index (68.9%).[13]

Cigarette smoke is a very high oxidant that can cause inflammation in the lungs and airways. The correlation between smoking and COPD is a dose-response relationship; the more the number of cigarettes smoked and the longer the smoking habit, the higher the risk of suffering from COPD.[2]

This study also assessed the quality of life of COPD patients who used indacaterol and tiotropium monotherapy as assessed by the SGRQ. The SGRQ is one of the measuring tools used to assess the quality of life of COPD patients that has been recognized in the medical field. The SGRQ contains 3 components, namely symptoms, activities and

impacts.

From the component of symptoms and impacts there were no significant differences between indacaterol dan tiotropium. Based on the activities component, tiotropium users had less activity limitations than indacaterol. Thus, on the overall score we obtained that the use of tiotropium monotherapy showed a better quality of life (76%) than indacaterol monotherapy (64%). After the statistical test, the difference between the two did not show any significance (P>0.05).

Different results were obtained by Buhl et al. in 2011 among 1477 patients with moderate and severe COPD who underwent a blind trial of once-daily dose of indacaterol and tiotropium for 12 weeks. The study revealed similar improvements in FEV_1 values on indacaterol and tiotropium groupsafter 12 weeks of treatment, with statistical tests proving indacaterol not inferior to tiotropium.

However, the reasons for these differences are still being investigated until now. Indacaterol and tiotropium may have different effects on overall lung volume, despite the similarity of FVC results. It would be interesting to compare the effects on inspiratory capacity. The two drugs have distinct bronchodilator effects on the small airways, possibly due to regional variations in the distribution of muscarinic and adrenergic receptors of the airways. This is what causes the difference in non-bronchodilator effects on pulmonary ventilation and pulmonary hemodynamics.

Another opinion suggests that the parasympathetic nervous system is a major component of airway smooth muscle tone and there is evidence proving that the cholinergic system is increased in COPD.[14–16] Therefore, COPD is recommended to be treated with anticholinergic drugs rather than beta-2 agonists.[15,16]

LIMITATION

Limitation of this study is writer could not rule out other factors that affect the quality of life of COPD patient such as age, gender, healthy lifestyle, etc.

CONCLUSION

In this study, tiotropium monotherapy showed a better quality of life than indacaterol monotherapy, but this difference was not statistically significant.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. Menteri Kesehatan Republik Indonesia. Pedoman Pengendalian Penyakit Paru Obstruktif Kronik. Keputusan Menteri Kesehatan Republik Indonesia, 1022/MENKES/SK/XI/2008 Indonesia; 2008 p. 4–39.
2. Perhimpunan Dokter Paru Indonesia. PPOK (Penyakit Paru Obstruktif Kronik): diagnosis dana Penetalaksanaan. 1st ed. Jakarta: UI-Press; 2016. 2 p.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 Report). Global Initiative for Chronic Obstructive Lung Disease. 2019.
4. World Health Organization. Chronic obstructive pulmonary disease (COPD) [Internet]. World Health Organization. 2017 [cited 2017 Oct 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
5. Jones R, Østrem A. Optimising pharmacological maintenance treatment for COPD in primary care. Prim Care Respir J. 2011;20(1):33–45.
6. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD

executive summary. Am J Respir Crit Care Med. 2007;176(6):532–55.
7. Gea J, Casadevall C, Pascual S, Orozco-Levi M, Barreiro E. Clinical management of chronic obstructive pulmonary disease patients with muscle dysfunction. J Thorac Dis. 2016;8(11):3379–400.
8. Flood P, Rathmell JP, Shafer S. Stoelting's pharmacology and physiology in anesthetic practice. 5th ed. Philadelphia: Wolters Kluwer; 2015. 370–371 p.
9. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. European Respiratory Journal. 2017;49(3):1700214.
10. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019;53(5):1900164.
11. Fukuchi Y. The aging lung and chronic obstructive pulmonary disease: similarity and difference. Proc Am Thorac Soc. 2009;6(7):570–2.
12. Soeroso NN, Zain-Hamid R, Sinaga BYM, Sadewa AH, Syafiuddin T, Syahruddin E, et al. The Role of CYP2A6 Genetic Polymorphism in Nicotine Dependence and Tobacco Consumption among Bataknese Male Smokers. Open Access Maced J Med Sci. 2018;6(5):864–6.
13. Broaddus VC, Mason RJ, Ernst JD, King TE, Lazarus SC, Murray JF, et al. COPD: clinical diagnosis and management. In: Murray & Nadel's Textbook of Respiratory Medicine, 2-Volume Set. 6th ed. Canada: Elsevier; 2015. p. 767–85.
14. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. Pulm Pharmacol Ther. 2010;23(4):257–67.
15. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J. 2003;22(4):672–88.
16. Gross NJ. Outcome measures for COPD treatments: a critical evaluation. COPD. 2004;1(1):41–57.

Original Article

The Compliance of Mask Use to Prevent the Spread of COVID-19 among High School Students in Banda Aceh

Novita Andayani,[1] Sarah Firdausa,[2] Teuku Romi Imansyah Putra,[3] Rezania Razali,[4] Syawqiyyah Salsabyla,[5] Murtaza Murtaza[5]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala/ dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala/ dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia
[3]Department of Parasitology, Faculty of Medicine, Universitas Syiah Kuala, Indonesia
[4]Department of Physiology, Faculty of Medicine, Universitas Syiah Kuala, Indonesia
[5]Students at the Faculty of Medicine, Universitas Syiah Kuala, Indonesia

Abstract

Background: COVID-19 is an air-borne disease caused by the SARS-CoV-2 virus that is spreading the globe. Masks are an attempt to break the chain of transmission of COVID-19. The purpose of this study is to examine the relationship between COVID-19 awareness and the use of masks to prevent the spread of COVID-19 among high school students in Banda Aceh City.

Methods: This study is an observational analytic study using a cross-sectional design. The number of samples is 402 students of SMA Negeri Banda Aceh. The subject recruitment used the proportional random sampling technique.

Results: This study was carried out from November 5 to November 21, 2020, with research questions distributed via Google Form. The Spearman correlation test was utilized in the statistical study. According to the findings, 69.4% of respondents had good knowledge of COVID-19, and 83.3% of respondents praised the use of masks. Statistical analysis reveals a p-value of 0.000 (p-value of 0.005) and a correlation coefficient of 0.275.

Conclusion: There is a modest correlation between Banda Aceh City Public High School students' understanding of COVID-19 and their wearing of masks to prevent COVID-19 transmission.

Keywords: Compliance, COVID-19, Knowledge, Students

Corresponding Author:
Sarah Firdausa | Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala, dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia | sarahfirdausa@unsyiah.ac.id

Submitted: November 25th, 2021
Accepted: August 8th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 282–8
https://doi.org/10.36497/jri.v42i4.254

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a pandemic triggered by infection with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, which impairs the human respiratory system. The symptoms of this illness are comparable to those of pneumonia.[1]

COVID-19 is more likely to infect older persons, particularly those with poor health, hence the danger of infection is greater among older individuals than among younger individuals. About 80% of deaths in China occurred in individuals 60 years old, whereas 0.1% of deaths happened in those less than 19 years old.[1]

In December of 2019, COVID-19 was first recorded in Wuhan, Hubei province, China. The coronavirus was recognized as novel coronavirus pneumonia by China's National Health Commission on February 7, 2020. The Corona Virus Study Group of the International Committee designated the coronavirus Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) on February 11, 2020. The World Health Organization (WHO) designated this new outbreak as COVID-19 and reported on March 12, 2020 that COVID-19 had attained pandemic status.[2]

COVID-19 is a novel infection that is rapidly spreading. This virus originated in China and

subsequently spread to various other nations.[3] On December 22, 2020, 77.850.785 cases of COVID-19, 1.711.847 deaths, and 54.723.861 recoveries were confirmed globally.[4] COVID-19 cases were found for the first time in Indonesia on March 2, 2020, while only two cases were detected.[5]

COVID-19 infections spread to Indonesia, causing the case mortality rate in Indonesia to reach 8.9% by the end of March 2020. It was the highest number of cases in Southeast Asia. On the December 22nd 2020, COVID-19 data from Indonesia indicated 678,125 confirmed cases, 20,257 deaths, and 552,722 recoveries.[4] At the same time, Aceh COVID-19 data revealed 8,620 confirmed cases, 342 deaths, and 7,435 recovered cases. While in Banda Aceh, there were 2,175 confirmed cases, 70 deaths, and 2,025 confirmed cases.[6]

The coronavirus can be spread between humans via respiratory secretions (droplets). To avoid and control COVID-19, the Indonesian government has developed a number of policies and guidelines. When leaving the house or engaging with individuals whose health status is unknown and who may spread COVID-19, one of the instructions provided by the Indonesian government is to wear a mask that covers the nose and mouth to the chin.[7] Masks are intended to prevent the spread of illness from the user to others and are also known as source control. Masks provide protection against infections spread through droplets, splashes, blood sprays, or body fluids.[8] Knowledge influences a person's compliance with masks, and it is vital to test this through a mask campaign in Indonesia. Compliance with masks must be evaluated by measuring the level of COVID-19 control achieved using a mask.[9]

The research conducted by Sari et al. (2020) in Ngronggah, Central of Java, and titled "The correlation between public knowledge and compliance with the use of masks in an effort to prevent COVID-19 disease" demonstrates that there is a significant correlation between public knowledge and compliance with the use of masks in an effort to prevent COVID-19. This study's sample consisted of 62 respondents. Her research instrument was a questionnaire. According to the findings, awareness of COVID-19 has a significant impact on patients' compliance with wearing masks.[10]

In spite of the fact that children and adolescents do not show the typical symptoms of COVID-19 like adults do, the coronavirus can however spread across these age groups. Children and adolescents who exhibit only mild symptoms or none at all have the potential to unintentionally infect individuals around them, so contributing to the transmission of the coronavirus and increasing the incidence of infection in their surrounding environments.[11]

Based on the aforementioned context, the researchers want to explore the association between the amount of information about COVID-19 and the use of masks to prevent the spread of COVID-19 among senior high school students in Banda Aceh.

METHODS

This study is a cross-sectional, observational, analytical investigation. From April to December of 2020, this study was conducted on senior high schools in Banda Aceh City.

The total number of students that participated in this study was 7,989, and they were all enrolled in grade X, as well as grades XI and XII at SMA Banda Aceh. The sample for this study was comprised of all of the high school students in Banda Aceh who fulfilled the inclusion criteria and did not fulfil any of the exclusion criteria.

Researchers utilize the Slovin formula to determine the number of samples:

$$n = \frac{N}{1 + N\ (d^2)}$$

Description:

n = total number of samples
N = population
d = the crucial proportion of the required activity limit (five percent).

Based on the data obtained, the number of samples in this study:

$$\mathrm{n} = \frac{7989}{1 + 7898\ (0{,}05^2)} = 399{,}94 = 400$$

The number of responders obtained from the above-mentioned calculation is 399,94. The number of responders was rounded to 400 by the researchers. The inclusion criteria for this study were Banda Aceh public high school students and pupils who understood how to fill out a Google form questionnaire. While the criteria for exclusion included public high school students who had issues accessing the internet or who did not have access to an online network, as well as public high school students who refused to participate as responders.

The sample for this study was selected using a combination of probability and proportional random sampling. The data that was utilized was primary data that was acquired through the use of online questionnaires that were distributed to students by means of Google Forms.

A univariate data analysis was performed on the collected information. In the form of a frequency distribution table, the data for each variable will be given. To determine the significance of the association between variables, Spearman Rank correlation test was used.

RESULTS

This research was carried out in 16 senior high schools around Banda Aceh, starting from SMAN 1 and going all the way up to SMAN 16. Out of a total student population of 7,989, only 402 students were selected for the sample because they fulfilled the inclusion criteria but did not fulfil the exclusion criterion.

An online survey was conducted from November 5, 2020, through November 21, 2020, in order to compile this information. The demographic information of respondents to the current study is included in Table 1, which includes their gender, age, students' class, and the name of their school.

According to Table 1, the majority of respondents were female; there were 278 females (69.2%) out of a total of 402. The bulk of 17-year-old respondents consisted of 329 pupils (81.8%), and the majority of respondents were from SMAN 3; there were 45 students (11.2%).

Table 1. Characteristics of Respondents

Characteristics	N	%
Gender		
Male	124	30.8
Female	278	69.2
Age		
16 years old	50	12.4
17 years old	329	81.8
18 years old	18	4.5
19 years old	5	1.2
School Name		
SMAN 1	35	8.7
SMAN 2	40	10.0
SMAN 3	45	11.2
SMAN 4	40	10.0
SMAN 5	32	8.0
SMAN 6	15	3.7
SMAN 7	40	10.0
SMAN 8	36	9.0
SMAN 9	27	6.7
SMAN 10	22	5.5
SMAN 11	28	7.0
SMAN 12	23	5.7
SMAN 13	3	0.7
SMAN 14	6	1.5
SMAN 15	3	0.7
SMAN 16	7	1.7
Total	402	100.0

Subjects' level of knowledge about COVID-19 are shown in Table 2. Table 3 depicts, in accordance with the findings of the research that has been carried out, the distribution and frequency of compliance with the usage of masks.

Table 2. Distribution and Frequency of Level of knowledge about COVID-19

Level of knowledge about COVID-19	N	%
Poor	4	1.0
Enough	119	29.6
Good	279	69.4
Total	402	100.0

Table 3. Distribution and Frequency of the Compliance of Using Masks

The Compliance of Using Masks	N	%
Disobedient	67	16.7
Compliant	335	83.3
Total	402	100.0

Table 4 displays the findings of the bivariate analysis and the link between the level of COVID-19 knowledge and mask use compliance.

Table 4. The Correlation between the Level of knowledge about COVID-19 and the Compliance of Using Masks

Level of knowledge	Compliance				Total		*P*	Correlation Coefficient (r)
	Disobedience		Obedience					
	n	%	n	%	n	%		
Poor	3	75,0	1	25,0	67	100,0		
Enough	36	30,3	83	69,7	335	100,0	0,0001	0,275
Good	28	10,0	251	90,0	402	100,0		

DISCUSSION

The study revealed that based on the distribution results of the degree of knowledge about COVID-19, the majority of SMAN 1 to SMAN 16 respondents in Banda Aceh have a high level of knowledge about COVID-19. There were 279 pupils (69.4%) who possessed a solid comprehension and grasp of COVID-19. This result is comparable to the findings of Yanti et al. (2020), who found that the community in Sumerta Kelod Village, Denpasar, Bali, had a good level of COVID-19 knowledge. Approximately 70% of villagers have a solid understanding of COVID-19.[12]

These findings were also validated by Suwandi et al. (2020), who found comparable outcomes. The majority of responders had a solid understanding of COVID-19. Approximately 76.6 percent of students at Advent Balikpapan High School had a solid comprehension of COVID-19.[13] Similarly, Saputra et al. (2020) discovered that boarding school students at Advent Indonesia University has an excellent degree of knowledge of COVID-19. There were 33.33 percent of pupils with a solid grasp of COVID-19.[14]

Based on these findings, it is evident that one of the measures to prevent the spread of COVID-19 demands a thorough awareness and familiarity with the virus. SARS-CoV-2 transmission cannot be prevented without an individual's knowledge of COVID-19. A person's capacity to determine and make sound decisions will be enhanced by their education.

In Banda Aceh senior high school students, the results of the measurement of their knowledge level of COVID-19 indicated that they comprehended nearly all of the questionnaire's statements well. However, two negative sentences were correctly answered by pupils. These are statements number 6 and 8, respectively. Statement number 6 indicated that anyone with close contact with a COVID-19-infected individual should be quarantined for 2–7 days. 74.9 percent of students correctly answered question number six. According to the World Health Organization, a person who comes into intimate contact with COVID-19 must be isolated for 14 days after the last verified exposure in order to prevent the widespread spread of the virus, as persons without symptoms may transmit the virus to others around them.[15]

In statement number eight, it was said that the number of COVID-19 cases would continue to rise and that it is fatal. This result indicated that 76.1 percent of senior high school pupils in Banda Aceh responded correctly to the question. Specifically, the elevated fatality rate induced by COVID-19 is attributable to a number of causes. Age is included in the individual factor, which is one of the factors. The old would suffer a biological ageing process characterized by diminished physical endurance, making their bodies prone to certain ailments. The elderly are therefore included in the susceptible population for COVID-19 infection. Then, a history of comorbidities such as diabetes, asthma, and cardiovascular disease is one of the causes of death in COVID-19-infected individuals.[16]

Formal education and information gleaned from mainstream media, newspapers, magazines, the Internet, and television are sources of knowledge. Motivation also affects knowledge since it can inspire curiosity about a topic through the pursuit of information sources.[17] This study revealed that senior high school students in Banda Aceh have a comprehensive understanding of COVID-19.

Based on the distribution of mask compliance findings, it was found that students in Banda Aceh from SMAN 1 to SMAN 16 complied to the mask use

policy. It was concluded that 335 pupils (or 83.3%) adhere to the mask use policy. These findings are supported by the findings of Sari et al. (2020), who discovered that 46 respondents (74.19%) out of 62 respondents willingly utilize masks.[10]

The findings of this study are confirmed by the findings of another study that was carried out by Ika and colleagues (2020). That study investigated the level of public understanding regarding COVID-19 as well as public behavior in the Wonohoso Regency. It was revealed that 72.2 percent of responders did, in fact, comply with the use of masks during the pandemic.[18]

The results of a study on mask compliance among senior high school students in Banda Aceh show that most pupils wore masks throughout the COVID-19 epidemic. To begin, pupils wear masks in public locations. Second, pupils constantly utilize masks to prevent COVID-19 transmission. Third, students continue to wear masks even while their peers do not. Fourth, students continue to use masks while driving or taking public transportation. Fifth, pupils get uneasy when they forget to wear a mask.

According to Notoatmodjo, the manner in which a person conducts themselves might have an effect on their compliance with rules. A person goes through a number of different behavioral stages. They are known as awareness, which occurs when something realizes or recognizes an object earlier, interest, which occurs when a person becomes interested in an object, and trial, which occurs when a person begins to try to do what they want in accordance with their knowledge, awareness, and stimulation.[18] As a result, it is possible that the behavior will encourage a decent level of adherence to the usage of masks among senior high school students in Banda Aceh.

With value of *P*=0.0001 and r=0.275, there is a weak correlation between COVID-19 knowledge and mask compliance in stopping the spread of COVID-19 among senior high school students in Banda Aceh. Based on the findings of the researchers' observations and the statistical results, the correlation coefficient value in this study is low because when respondents filled out the questionnaire, a large proportion of them properly answered the question concerning their level of awareness about COVID-19 and mask compliance. However, in actual life, some responders refused to wear masks. According to the distribution, the majority of respondents with a decent degree of understanding were willing to use masks; there were 251 people (90.0%). These findings are corroborated by Sari's et al. research which found a link between knowledge and compliance with utilizing masks in COVID-19 prevention efforts.[10]

According to Suryaningnorma et al., the variable of knowledge has the potential to have a considerable influence on both compliance behavior and knowledge. There is a favorable association between this compliant behavior and the outcome. It may be possible for a person to be more compliant with the requirement that they wear masks if they have a deeper understanding of COVID-19. Notoatmodjo provides additional evidence in support of this thesis, stating that in order to actualize one's obedience, one must first amass a significant amount of knowledge and information regarding the subject in question.[19]

According to the statement above, SMAN Kota Banda Aceh students' knowledge of COVID-19 correlated with their use of masks.

LIMITATION

The study employs a cross-sectional approach, making it difficult to establish a cause-and-effect relationship because it only represents a one-time measurement of alleged causation. Furthermore, the distribution of the questionnaire is virtually done to the respondent, potentially reducing the objectivity of the study because it may result in a social desirability bias and a tendency to improve the answers. Circumstances influencing respondents' compliance in using masks are not only the level of education, experience, and awareness of COVID-19, but also the environmental aspects, behaviors of individuals around their homes, schools, or workplaces, and other factors which were not explored in this study.

CONCLUSION

The willingness of students to use masks to limit the transmission of COVID-19 among senior high school students in Banda Aceh City is correlated with their level of knowledge about the virus.

ACKNOWLEDGMENTS

The authors would like to thank the respondents who have kindly participated in the study and the supporting personnel whose assistance was invaluable in preparing the manuscript.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(12):343–6.
2. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty. 2020;9(1).
3. Hua J, Shaw R. Corona virus (COVID-19) "infodemic" and emerging issues through a data lens: The case of china. International Journal of Environmental Research and Public Health 2020, Vol 17, Page 2309. 2020;17(7):2309.
4. Worldometer. COVID Live - Coronavirus Statistics [Internet]. Worldometer. 2020 [cited 2020 Dec 22]. Available from: https://www.worldometers.info/coronavirus/
5. del Rio C, Malani PN. COVID-19—New insights on a rapidly changing epidemic. JAMA. 2020;323(14):1339–40.
6. Dinas Kesehatan Pemerintah Aceh. Aceh tanggap COVID-19 [Internet]. Dinas Kesehatan Pemerintah Aceh. 2020 [cited 2020 Dec 22]. Available from: https://covid19.acehprov.go.id/
7. Kementrian Kesehatan Republik Indonesia. Pedoman pembatasan sosial berskala besar dalam rangka percepatan penanganan corona virus disease 2019 (COVID-19). Peraturan Menteri Kesehatan Nomor 9 Tahun 2020. [Jakarta]: Kementrian Keseharan Republik Indonesia; 2020.
8. World Health Organization. Advice on the use of masks in the community, during home care, and in health care settings in the context of COVID-19. 2020. p. 1–2.
9. Zhong BL, Luo W, Li HM, Zhang QQ, Liu XG, Li WT, et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. Int J Biol Sci. 2020;16(10):1745.
10. Sari DP, 'Atiqoh NS. Hubungan antara pengetahuan masyarakat dengan kepatuhan penggunaan masker sebagai upaya pencegahan penyakit COVID-19 di ngronggah. Infokes: Jurnal Ilmiah Rekam Medis dan Informatika Kesehatan. 2020;10(1):52–5.
11. Debiasi RL, Delaney M. Symptomatic and asymptomatic viral shedding in pediatric patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Under the surface. JAMA Pediatr. 2021;175(1):16–8.
12. Yanti NPED, Nugraha IMADP, Wisnawa GA, Agustina NPD, Diantari NPA. Gambaran pengetahuan masyarakat tentang COVID-19 dan perilaku masyarakat di masa pandemi COVID-19. Jurnal Keperawatan Jiwa. 2020;8(3):491–504.
13. Suwandi GR, Malinti E. Hubungan tingkat pengetahuan dengan tingkat kecemasan terhadap COVID-19 pada remaja di SMA advent balikpapan. Malahayati Nursing Journal. 2020;2(4):677–85.

14. Saputra AW, Simbolon I. Hubungan tingkat pengetahuan tentang COVID-19 terhadap kepatuhan program lockdown untuk mengurangi penyebaran COVID-19 di kalangan mahasiswa berasrama universitas advent indonesia. Nutrix Journal. 2020;4(2):1–7.
15. World Health Organization. Transmission of SARS-CoV-2: Implications for infection prevention precautions. 2020. p. 1–10.
16. Matla Ilpaj S, Nurwati N. Analisis pengaruh tingkat kematian akibat COVID-19 terhadap kesehatan mental masyarakat indonesia. Focus: Jurnal Pekerjaan Sosial. 2020;3(1):16–28.
17. Sukesih, Usman, Budi S, Sari DNA. Pengetahuan dan sikap mahasiswa kesehatan tentang pencegahan COVID-19 di indonesia. Jurnal Ilmu Keperawatan dan Kebidanan. 2020;11(2):258–64.
18. Aula SKN. Peran tokoh agama dalam memutus rantai pandemi COVID-19 di media online indonesi. Living Islam: Journal of Islamic Discourses. 2020;3(1):125–48.
19. Suryaningnorma VS. Analisis terhadap faktor-faktor yang mempengaruhi kepatuhan obat asma inhalasi: Studi pada pasien rawat jalan poli asma RSU dr. soetomo surabaya [Skripsi]. [Surabaya]: Universitas Airlangga; 2006.

Original Article

Cost-Effectiveness Analysis of Budesonide/Formoterol and Fluticasone/Salmeterol for Stable Chronic Obstructive Lung Disease

Amelia Lorensia,[1] Monica Dyah Puspitasari,[1] Soedarsono,[2] Rivan Virlando Suryadinata[3]

[1]Department of Clinical-Community Pharmacy Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia
[2]Departement of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Public Health Faculty of Medicine, Universitas Surabaya, Surabaya, Indonesia

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is one of the four largest types of non-communicable diseases in the world, requiring long-term and routine treatment. Treatment with the inhalation route is in the form of a dry-powder inhaler (DPI) which is easy to use and carry. Combination of corticosteroid and long-acting beta-2 agonist (LABA) in the form of DPI available in Indonesia are budesonide/formoterol and salmeterol/fluticasone. The purpose was to identify therapy was more cost-effective between budesonide/formoterol than fluticasone/salmeterol in clinical symptoms using COPD assessment test (CAT) value and lung function in FEV_1/FVC (Forced Expiratory Volume in First Seconds/Forced Vital Capacity) ratio.

Methods: This research study was pre-post design with cost-effectiveness analysis, in outpatient COPD patients in a hospital in Gresik Regency, from October 2019 to January 2020. There were two outcomes of respondents in this study, namely lung function seen from the value of FEV_1, and clinical symptoms seen from the value of CAT. The study used hospital perspective.

Results: There were 38 respondents involved. Fluticasone/salmeterol therapy was more effective than the budesonide/formoterol group in improving FEV_1/FVC ratio, while budesonide/formoterol was more effective than the fluticasone/salmeterol group in improving clinical symptoms by CAT assessment. The average cost effectiveness ratio (ACER) value of lung function between the fluticasone/salmeterol group (IDR.176.465/Liter) was lower than that of budesonide/formoterol (IDR.296.832/Liter). The ACER clinical symptoms value between the fluticasone/salmeterol group (IDR.16,283/score) was smaller than that of budesonide/formoterol (IDR.17,340/score).

Conclusion: Fluticasone/salmeterol was more cost-effective than budesonide/formoterol in improving lung function. Meanwhile, for clinical symptoms, fluticasone/salmeterol was trade-off with budesonide/formoterol.

Keywords: COPD; FEV_1/FVC ratio; inhaled corticosteroid; Long-acting Beta-2 Agonist

Corresponding Author:
Amelia Lorensia | Department of Clinical Community Pharmacy, Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia | amelia.lorensia@staff.ubaya.ac.id; amelia.lorensia@gmail.com

Submitted: September 8th, 2022
Accepted: October 4th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 289–97
https://doi.org/10.36497/jri.v42i4.378

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by airflow limitation that is not fully reversible. The airway limitation is usually progressive and is associated with an inflammatory response due to noxious substances or gases. COPD is one of the respiratory system diseases that is the cause of high morbidity and mortality in the world.[1] COPD comorbidities will result in cardiovascular disease, bronchial cancer, lung infections, thromboembolic disorders, the presence of asthma, hypertension, osteoporosis, joint pain, depression and anxiety.[2]

Respiratory diseases such as asthma and COPD require long-term and regular treatment. The route of drug administration is generally by inhalation because the effect is directly on the target organ in the lungs and causes side effects that tend to be smaller than other routes, because the drug works topically so it does not require larger doses as in systemic administration. One of the maintenance treatments for COPD is a combination of LABA and inhaled corticosteroid (ICS) in one package.[3]

Inhalers were an important drug delivery device in COPD because they enter the respiratory system directly and have fewer side effects.[4] The DPI type inhaler was relatively easier than MDI because

it does not require coordination between pressing and inhaling. Dry-powder inhaler (DPI) is in the form of a fine powder that acts directly on the respiratory tract of the bronchioles so that the effect of the drug can be faster and side effects that often appear in systemic treatment.[5] The combination of ICS and LABA in the form of DPI in Indonesia was combination of budesonide/formoterol and salmeterol/fluticasone.

The total direct cost of COPD diagnosis-treatment for each year from 2012 to 2016 in Turkey. The direct costs of the patients who were admitted to step 1, step 2, and step 3 health care centers between 2012 and 2016 increased by 41%; the increase was 60% and 24%, for inpatient and outpatient groups respectively. In the year 2016, the direct total cost was 1003TL ($332) per patient. For the inpatient group, the mean number of hospitalizations per patient, mean number of hospitalization days, and the mean cost per hospitalization were 0.4, 6.5, and 1926TL ($637), respectively.[6]

In Indonesia, a previous study on COPD inpatients at Sukoharjo General Hospital,[7] showed that the average cost of COPD for severe severity was IDR.1,349,671 for the three types of financing, for the very severe level, the types of general financing, JAMKESMAS (*Jaminan Kesehatan Masyarakat*/ Community Health insurance) and JAMKESDA (*Program Jaminan Kesehatan Masyarakat Daerah*/ Regional Public Health Insurance Program) were IDR.1,051,955.5, ID.1,815,859 and IDR. 1,589,706.5. The results showed that the average real cost of COPD treatment was lower and significantly different from the cost of the INA-CBG package. While the cost of outpatient treatment had not been found.

Based on the results of the above study, it was more directed to the cost of therapy in COPD patients, but not many studies had examined the effectiveness compared to the costs incurred by patients with COPD and family.[8,9] The implementation of these studies can give clinicians confidence in providing therapy rationally (effectively and efficiently) and reduce costs incurred by patients or their families.[10]

This method of cost-effectiveness analysis was the simplest, easiest and most applicable method in its application. The most appropriate pharmacoeconomic method for analysis was cost-effectiveness analysis (CEA) because of comparing therapeutic outcomes that can be measured in the same unit and costs are measured in currency.[11] CEA was most often used for economic analysis of health economics and is often used in drug therapy.[12] Outcomes of therapy in CEA can be investigated with the COPD Assessment Test (CAT) and spirometry.[13]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends a multidimensional assessment called the Combined COPD assessment that combines the degree of obstruction or a history of acute exacerbations and an assessment of the patient's symptoms/impacts.[14] The spirometry classification assessment alone often does not represent the impact of COPD on the patient's quality of life.[15]

The quantitative assessment of symptoms, represented by the CAT, was aimed at evaluating the health impact on sufferers. This instrument has been validated in several European countries as well as the United States and has a good correlation with the more complex St George Respiratory Questionnaire (SGRQ). The CAT which has been translated into 61 languages and in Asia has been validated together, including in Indonesia. This test contains 8 questions with a score between 0–5 so that the total score will range between 0 and 40. The higher a person's score, the higher the impact of COPD on the patient's health status. Filling out the questionnaire in the CAT is done directly by the patient.[16]

Many parameters and methods are available for the purposes of assessing lung function. Impaired lung function can be tested using spirometry, the value used to detect the disorder is characterized by a decrease in Forced Vital Capacity (FVC) and Forced Expiratory Volume in First Seconds (FEV_1). Spirometry is an examination technique to determine lung function. The patient is asked to blow as hard as possible through a device that is connected to a spirometer machine which will automatically calculate the force, velocity and volume of air

expelled, so that the condition of the patient's lung function can be known.[17–19] The purpose of this study was to find out which therapy was more cost effective between budesonide/formoterol than fluticasone/salmeterol in terms of clinical symptoms using the CAT questionnaire and spirometry (FEV_1/FVC ratio).

METHODS

The research design was prospective observational study with pre-post design by conducting comparative study between budesonide/formoterol versus fluticasone/salmeterol in outpatient COPD patients in a hospital in Gresik Regency, from October 2019 to January 2020. The study used hospital perspective. And had received a certificate of ethics from the University of Surabaya No. 108/KE/XI/2019.

The effectiveness of budesonide/formoterol and fluticasone/salmeterol with FEV_1/FVC ratio, CAT questionnaire, and the incidence of drug side effects. Side effects were adverse drug reaction (ADR) and monitored for 3 months, namely oropharyngeal candidiasis (signs: white patches or plaques on the tongue and mucous membranes of the mouth) and pharyngitis (signs: sore throat, difficulty swallowing). The costs used were direct medical costs, including drugs, medical service, physical service, laboratory service, hospital service, and costs incurred to treat the side effects of COPD drugs that arise. The cost of health services listed on the patient's payment receipt.

The population was all patients who went to the pulmonary polyclinic of hospital X in Gresik between October 2019 and January 2020. The samples were all COPD patients who had used budesonide/formoterol or fluticasone/salmeterol therapy for 3 months, with age criteria >40 years, and willing to be involved in the research for 3 months. The sampling method was carried out using purposive sampling method.

The instruments used in the study were: CAT for the assessment of lung function. Consists of 8 questions with a score of 0-5 per question (Total scores ranged between 0 and 40). The greater a person's score, the higher the impact of COPD on the patient's health status. Assessment of lung function/physiology using spirometry, the value used to detect impaired lung function/physiology is marked by a decrease in FEV_1 and FVC.

Monitoring therapy for 3 months on the appearance of side effects of oropharyngeal candidiasis and pharyngitis with the Naranjo Scale. Pharmacoeconomic analysis by calculating ACER (Average Cost Effectiveness Ratio) by calculating the ratio of total cost to outcome, lung function (FEV_1/FVC ratio) and clinical symptoms (CAT). Then proceed with a different test to see the outcome, namely FEV_1/FVC ratio with t-test or Mann-Whitney test (ratio data scale) and CAT value with chi-square test (ordinal data scale).

RESULTS

The results of data collection on COPD patients receiving budesonide/formoterol and fluticasone/salmeterol therapy at the pulmonary polyclinic of X Hospital in Gresik from October 2019 to January 2020. There were 38 respondents involved in the study.

From Table 1, it can be seen that the characteristics of respondents based on gender, respondents were more male (52.63%) than female (47.37%). Characteristics of age, the largest number of respondents were 61-70 years old (50.00%). In terms of type of work, more respondents are not working or have retired. Most respondents are those who have quit smoking (52.63%). As for the characteristics of the incidence of drug side effects, neither side effects were found at all.

There were two outcomes of respondents in this study, namely lung function seen from the value of FEV_1 and clinical symptoms seen from the value of CAT which was shown in Table 2. Pulmonary function in both the budesonide/formoterol and fluticasone/salmeterol groups by looking at the FEV_1/FVC obtained P=0.007 explained that there was a significant difference between lung function in the two groups budesonide/formoterol and

fluticasone/salmeterol. Meanwhile, for clinical symptoms by looking at the patient's CAT score, *P*=0.880 explained that there was no significant difference between the clinical symptoms of budesonide/formoterol and fluticasone/salmeterol.

In this study, the effectiveness of treatment was assessed based on a comparison of lung function and COPD symptoms. The total FEV_1/FVC ratio in the fluticasone/salmeterol group (28.42 liters) was greater than in the budesonide/formoterol group (20.33 liters). The average FEV_1/FVC ratio in the fluticasone/salmeterol group (1.58 liters) was greater than that in the budesonide/formoterol group (1.02 liters). The total CAT score in the budesonide/formoterol group (348) was greater than that in the fluticasone/salmeterol group (308). The mean FEV_1/FVC ratio in the budesonide/formoterol group (17.4) was greater than in the fluticasone/salmeterol group (17.11). Fluticasone/salmeterol therapy was more effective than the budesonide/formoterol group in improving lung function (FEV_1/FVC ratio), while budesonide/formoterol was more effective than the fluticasone/salmeterol group in improving clinical symptoms by CAT assessment (Table 2).

Mann-Whitney test on the effectiveness of the value of FEV_1/FVC ratio, it was known that value of *P*=0.007 was smaller than the probability (0.05.) Thus, it can be said that there was a significant difference between the use of fluticasone/salmeterol and budesonide/formoterol group (Table 2 and Figure 1).

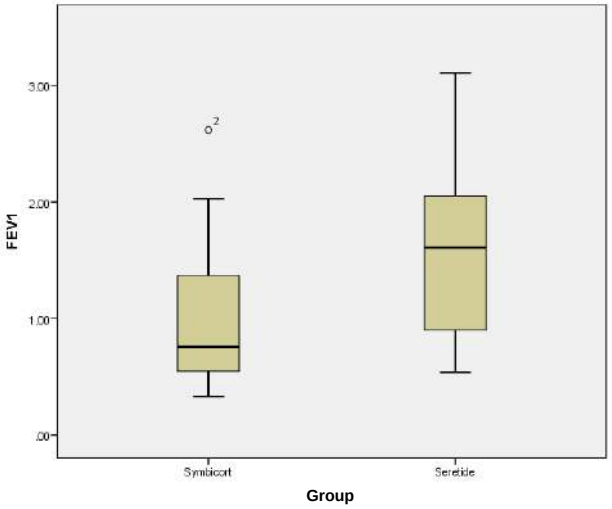

Figure 1. Test of Differences in Effectiveness of FEV1/FVC Ratio with Ratio Scale

Table 1. Characteristics of Respondents

Characteristics		Group		*P*
		Budesonide/formoterol (n:20)	Fluticasone/salmeterol (n:18)	
Gender	Man	14	17	0.052
	Female	6	1	
Age (years)	40–50	1	0	
	51–60	7	4	
	61–70	8	11	0.526
	71–80	3	3	
	>80	1	0	
Job	Civil servant	0	1	
	General employees	3	1	0.441
	Self-employed	4	6	
	Other	13	10	
Smoking History	Quit smoking	7	13	
	Smoke	2	0	0.005*
	Did not smoke	11	5	
Drug Side Effects	Exist	0	0	1.000
	No	20	18	

Note= *) There was difference between the two groups

Table 2. Respondent Outcome Profile

Outcome		Group		*P*
		Budesonide/formoterol (n:20)	Fluticasone/salmeterol (n:18)	
Lung Function (Liters)	Total FEV1/FVC ratio	20.33	28.42	0.007
	Average FEV1/FVC ratio	1.02	1.58	
Clinical Symptoms	Total CAT	348	308	0.880
	Average	17.4	17.11	

Table 3. Cost Profile

Cost (in rupiah)		Group:		*P*
		Budesonide/formoterol (n:20)	Fluticasone/salmeterol (n:18)	
Direct medical cost (IDR)	Drug cost	154,424	142,737	
	Medical service	24,094	12,655	
	Physical service	40,000	40,000	0.069
	Laboratory service	58,212	58,212	
	Hospital service	25,000	25,000	
Average total cost (IDR)		301,730	278,604	

Table 4. Calculation Results of Cost-Effectiveness Analysis

CEA Calculation	Group:			
	Budesonide/formoterol (n:20)		Fluticasone/salmeterol (n:18)	
ACER lung function (IDR/Liter)	IDR	296,832 /Liter	IDR	176,465/Liter
ACER clinical symptoms	IDR	17,340/score	IDR	16,283/ score

There were 38 data that are all processed (no data is missing or missing), so the level of validity was 100%. The cross table that contained the relationship between drug therapy variables and CAT values. With ordinal data scale, fluticasone/salmeterol therapy (n:18) consisted of 5 people with mild group and 13 people with moderate-severe level. And budesonide/formoterol therapy (n:20) consisted of 6 people with mild group and 14 people with moderate-severe level. In the Pearson Chi-Square section, the value of *P*=0.880, it can be concluded that there was no significant relationship between the drug and the CAT value. This meaned that budesonide/formoterol and fluticasone/salmeterol have no correlation with CAT values (Figure 2).

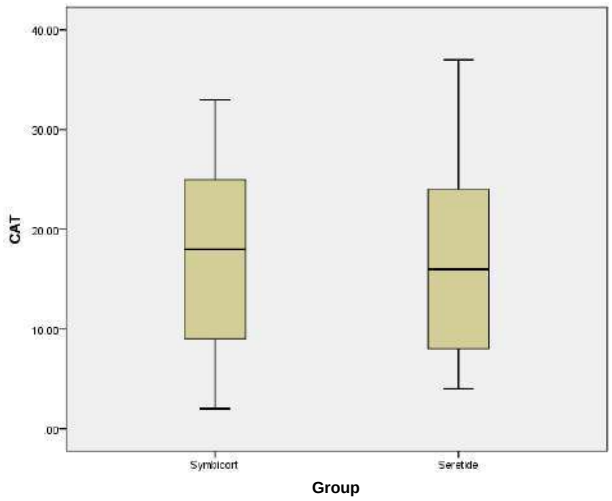

Figure 2. Test of Differences in Effectiveness of Clinical Symtoms Ratio with Ordinal Scale

It was known that the costs for the two groups resulted *P*=0.069 explaining that there was an insignificant difference between the costs of budesonide/formoterol and fluticasone/salmeterol. The costs used are direct medical costs, including drugs, medical service, physical service, laboratory service, and hospital service. Drug costs were the largest of the total costs. Average total cost in the budesonide/formoterol group (IDR. 301,730) was greater than in the fluticasone/salmeterol group (IDR. 278,604) (Table 3).

The ACER value of lung function between the fluticasone/salmeterol group (IDR. 176.465/Liter) was lower than that of budesonide/formoterol (IDR. 296.832/Liter). And the ACER clinical symptoms value between the fluticasone/salmeterol group (IDR. 16,283/score) was smaller than that of budesonide/formoterol (IDR. 17,340/score) (Table 4). It can be concluded that fluticasone/salmeterol was more cost-effective than budesonide/formoterol in improving lung function (FEV1/FVC ratio). Meanwhile, for clinical symptoms, fluticasone/salmeterol was a trade-off with budesonide/formoterol.

DISCUSSION

There were more male respondents than female (Table 1). COPD patients were more common in men. COPD was a condition in which the lung airways become inflamed and narrowed and the air sacs became damaged. It was a major cause of morbidity and mortality around the globe. Smoking cessation was particularly important in male COPD patients because of much higher proportion of smokers and are more likely to have cough and sputum.[20] These findings signify the importance of identifying and implementing gender-tailored

symptom management strategies to relieve symptom burden in COPD patients to enhance their quality of life.[21]

Age was often listed as a risk factor for COPD, but it was not clear whether healthy aging affects COPD or whether age reflects the cumulative amount of exposure over a lifetime. Patients with COPD at an early age or who had a strong relative history of COPD should be screened for risk for AAT deficiency, and if AAT concentrations are low, genetic (DNA) testing may be necessary.[9]

The highest age range was 61-70 years (Table 1), for elderly. COPD morbidity increases with age. Although the development of comorbid COPD can occur at a younger age. COPD was also more common at the age of >40 years than <40 years and was more common in males than females. Most of the increase in COPD mortality was due to the growing epidemic of smoking, decreased mortality from other common causes of death such as ischemic heart disease, infectious diseases.[22] In developing countries, deaths from COPD are also increasing, this was associated with an increase in the number of people who consume cigarettes. COPD had been considered as a disease affecting the elderly, with a preponderance in male smokers.[22,23]

In the budesonide/formoterol group, most did not smoke (55.00%). While in the fluticasone/salmeterol group, most of them had stopped smoking (72.22%). A person who quits smoking showed an improvement in lung function in the future. This was consistent with a previous study that increased FEV_1 in the first 6 and 12 weeks, in COPD patients after smoking cessation. In addition, both COPD patients and those with normal baseline respiratory function who quit smoking showed a significant increase in pulmonary transfer factor values for carbon monoxide from 6 weeks to 1 year of follow-up.[24] Side effects did not appear in all respondents. ICS together with LABA reduced the risk of exacerbations in COPD. ICS, however, do have side effects where an increased risk of pneumonia is probably the most clinically important one.[25]

COPD is diagnosed through spirometry, which can detect COPD even in people who do not yet have symptoms.[26] Currently, there is no cure for COPD, although available therapy can improve symptoms, quality of life, and prevent acute worsening of the disease. Pulmonary function in both groups of budesonide/formoterol and fluticasone/salmeterol by looking at the value of FEV1/FVC ratio obtained P=0.007 explained that there was a significant difference between lung function in the two groups. As for clinical symptoms, by looking at the CAT score obtained P=0.880, it explained that there was no significant difference between clinical symptoms and the CAT value between budesonide/formoterol and fluticasone/salmeterol. Fluticasone/salmeterol was more cost-effective than budesonide/formoterol in improving lung function (FEV_1/FVC ratio). Meanwhile, for clinical symptoms, fluticasone/salmeterol was a trade-off with budesonide/formoterol (Table 4).

The effectiveness parameter between lung warts (FEV_1) and symptoms has a low correlation. COPD symptoms exhibit high seasonal, weekly, and daily variability. Shortness of breath is a hallmark symptom of COPD and there is increasing evidence to suggest that the overall symptom burden (which may also include cough, sputum production, wheezing, and chest tightness) has a substantial adverse impact on health status, quality of life, and activities of daily living, and also contributes to increased anxiety and depression rates, increased risk of exacerbations, and poorer disease prognosis. Pulmonary function, on the other hand, shows circadian variation even in healthy individuals, so it is perhaps not surprising that many patients with COPD experience variations in their symptoms throughout the day, with symptoms being most severe in the morning and evening. There was a statistically significant correlation between total lung capacity and COPD severity.[27]

In this study, only direct medical costs were involved, according to the hospital's perspective. COPD results in substantial costs to the health system, particularly in relation to its moderate to severe stage and its associated exacerbations and complications. It is important to strengthen the health

system with a health monitoring, evaluation and education model that allows these patients to remain stable to avoid decompensation and subsequent hospitalization. In the case of very common chronic diseases, it is important to measure the social and financial magnitude of the disease in all areas (direct and indirect costs, health and non-medical costs, labor losses and intangible costs).[10]

It is important to note that cost variability in reported outcomes is largely a consequence of methodological divergences and research objectives impacting the type of cost in the way resources are identified, measured, valued, and consumed by COPD patients in various studies.[10]

ACER of lung function between the fluticasone/salmeterol group was lower than that of budesonide/formoterol, and the ACER of clinical symptoms between the fluticasone/salmeterol group was smaller than that of budesonide/formoterol. ACER represents the average cost required to obtain clinical results. Based on previous research by Tamminen et al. to explore the cost-effectiveness of budesonide/formoterol maintenance and reliever therapy as compared to fixed combination therapies (budesonide/formoterol and salmeterol/fluticasone) with terbutaline as needed in the treatment of asthma in Finland. Budesonide/formoterol maintenance and reliever therapy may be considered in the treatment of moderate-to-severe asthma instead of conventional treatment with combination products in view of its good clinical efficacy and a high probability of cost-effectiveness in the Finnish setting.[28]

While other studies that tested the effectiveness, by Robert et al, of the 6770 patients (3385 budesonide/formoterol and 3385 fluticasone/salmeterol), fewer budesonide/formoterol patients had claims for short-acting beta agonists (SABA) (34.7% vs 39.5%; *P*<0.001) and ipratropium (7.8% vs 9.8%, *P*<0.005) than fluticasone/salmeterol patients, but no substantial differences were seen in other clinical outcomes including tiotropium or nebulized SABA claims, COPD-related outpatient visits, or exacerbation events. There were no significant differences in total COPD-related medical costs in the 6-month period after initiation of combination therapy.[29]

LIMITATION

The limitations of this study were the presence of several factors that can affect pulmonary function scores and clinical symptoms other than inhaler therapy used, such as the severity of COPD, and other therapies used for COPD or other therapies.

CONCLUSION

Fluticasone/salmeterol therapy was more cost-effective than budesonide/formoterol in improving lung function in FEV_1/FVC ratio. And fluticasone/salmeterol was a tradeoff with budesonide/formoterol in clinical symptoms in CAT score. No drug side effects were found between fluticasone/salmeterol and budesonide/formoterol.

REFFERENCE

1. Yawn BP, Mintz ML, Doherty DE. GOLD in practice: Chronic obstructive pulmonary disease treatment and management in the primary care setting. Int J Chron Obstruct Pulmon Dis. 2021;16:289–99.
2. Iglesias JR, Díez-Manglano J, García FL, Peromingo JAD, Almagro P, Aguilar JMV. Management of the COPD patient with comorbidities: An experts recommendation document. Int J Chron Obstruct Pulmon Dis. 2020;15:1015.
3. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–82.
4. Jardim JR, Nascimento OA. The importance of inhaler adherence to prevent COPD exacerbations. Medical Sciences. 2019;7(4):54.
5. Shetty N, Cipolla D, Park H, Zhou QT. Physical stability of dry powder inhaler formulations. Expert Opin Drug Deliv. 2020;17(1):77–96.

6. Ozdemir T, Kilic H, Demirci NY, Ozdilekcan C, Bektemur G, Turkkani MH, et al. Five-year trends in direct costs of chronic obstructive pulmonary disease in turkey: COPDTURKEY-3. Turk Thorac J. 2021;22(5):393–8.
7. Alaydrus S. Analisis biaya pengobatan penyakit paru obstruktif kronik pasien rawat inap rumah sakit umum daerah kabupaten sukoharjo. Jurnal Ilmiah Farmasi Farmasyifa. 2020;3(1):51–61.
8. Voorham J, Corradi M, Papi A, Vogelmeier CF, Singh D, Fabbri LM, et al. Comparative effectiveness of triple therapy versus dual bronchodilation in COPD. ERJ Open Res. 2019;5(3):00106–2019.
9. Choi JY, Rhee CK. Diagnosis and treatment of early chronic obstructive lung disease (COPD). J Clin Med. 2020;9(11):1–20.
10. Gutiérrez Villegas C, Paz-Zulueta M, Herrero-Montes M, Parás-Bravo P, Madrazo Pérez M. Cost analysis of chronic obstructive pulmonary disease (COPD): A systematic review. Health Econ Rev. 2021;11(1):31.
11. Franklin M, Lomas J, Richardson G. Conducting value for money analyses for non-randomised interventional studies including service evaluations: An educational review with recommendations. Pharmacoeconomics. 2020;38(7):665–81.
12. Tonin FS, Aznar-Lou I, Pontinha VM, Pontarolo R, Fernandez-Llimos F. Principles of pharmacoeconomic analysis: The case of pharmacist-led interventions. Pharm Pract (Granada). 2021;19(1):1–10.
13. Qu S, You X, Liu T, Wang L, Yin Z, Liu Y, et al. Cost-effectiveness analysis of COPD screening programs in primary care for high-risk patients in china. NPJ Prim Care Respir Med. 2021;31(1):28.
14. Patel AR, Patel AR, Singh S, Singh S, Khawaja I. Global initiative for chronic obstructive lung disease: The changes made. Cureus. 2019;11(6):e4985.
15. Fazleen A, Wilkinson T. Early COPD: Current evidence for diagnosis and management. Ther Adv Respir Dis. 2020;14:1753466620942128.
16. Stridsman C, Svensson M, Johansson Strandkvist V, Hedman L, Backman H, Lindberg A. The COPD assessment test (CAT) can screen for fatigue among patients with COPD. Ther Adv Respir Dis. 2018;12:1753466618787380.
17. Sim YS, Lee JH, Lee WY, Suh DI, Oh YM, Yoon JS, et al. Spirometry and bronchodilator test. Tuberc Respir Dis (Seoul). 2017;80(2):105–12.
18. Gold WM, Koth LL. Pulmonary function testing. In: Murray and Nadel's Textbook of Respiratory Medicine. Elsevier; 2016. p. 407–35.
19. Hoesterey D, Das N, Janssens W, Buhr RG, Martinez FJ, Cooper CB, et al. Spirometric indices of early airflow impairment in individuals at risk of developing COPD: Spirometry beyond FEV1/FVC. Respir Med. 2019;156:58–68.
20. Lorensia A, Pratama AM, Hersandio R. Knowledge and attitudes on smoking cessation of e-cigarettes: A mixed-methods study of pharmacy students in surabaya, indonesia. J Prev Med Hyg. 2022;62(4):E918–25.
21. Zhang H, Wu F, Yi H, Xu D, Jiang N, Li Y, et al. Gender differences in chronic obstructive pulmonary disease symptom clusters. Int J Chron Obstruct Pulmon Dis. 2021;16:1101–7.
22. Divo MJ, Celli BR, Poblador-Plou B, Calderón-Larrañaga A, de-Torres JP, Gimeno-Feliu LA, et al. Chronic obstructive pulmonary disease (COPD) as a disease of early aging: Evidence from the EpiChron Cohort. PLoS One. 2018;13(2):e0193143.
23. Moryson W, Stawinska-Witoszynska B. Premature mortality due to chronic obstructive pulmonary disease (COPD) in Poland. Medicina (B Aires). 2021;57(2):1–7.
24. Gülşen A. Pulmonary function changes in chronic obstructive pulmonary disease patients according to smoking status. Turk Thorac J. 2020;21(2):80–6.
25. Janson C. Treatment with inhaled corticosteroids in chronic obstructive pulmonary disease. J Thorac Dis. 2020;12(4):1561–9.
26. Lorensia A, Muntu CM, Suryadinata RV, Septiani R. Effect of lung function disorders and physical

activity on smoking and non-smoking students. J Prev Med Hyg. 2021;62(1):E89–96.

27. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir Res. 2017;18(1):1–11.
28. Tamminen K, Laine J, Soini E, Martikainen J, Kankaanranta H. Cost-effectiveness analysis of budesonide/formoterol maintenance and reliever therapy versus fixed combination treatments for asthma in Finland*. Curr Med Res Opin. 2008;24(12):3453–61.
29. Roberts M, Mapel D, Petersen H, Blanchette C, Ramachandran S. Comparative effectiveness of budesonide/formoterol and fluticasone/salmeterol for COPD management. J Med Econ. 2011;14(6):769–76.

Original Article

Clinical Profile of COVID-19 Patients from March 2020 to March 2021 in Abepura Regional General Hospital (RSUD Abepura), Papua

Yenny Belinda Jioe, Helena Pakiding, Nancye Lorein, Dessy Yuliana, Febrianti Manga Mangontan, Fergina Stefany Berhitu

Department of Pulmonology and Respiratory Medicine, Abepura Regional General Hospital, Papua, Indonesia

Abstract

Background: SARS-COV-2 infection has widely spread and caused high morbidity and mortality rates. Despite more than one year of the COVID-19 pandemic in Indonesia, there is no scientific report regarding COVID-19 from Papua. This study aims to assess the clinical profile of COVID-19 patients in Abepura Regional General Hospital (RSUD Abepura), Papua.

Methods: We retrospectively recorded patients' age, sex, race, comorbidities, admitting and principal diagnoses, length of stay (LOS), and outcome (deceased/discharged) from the medical records from March 2020 to March 2021. Categorical data were described in frequencies and percentage, while numerical data were described in mean±SD or median and IQR. We analyzed the association between independent variables (age, sex, race, comorbidities, and diagnoses) with LOS and mortality rate.

Results: We included 461 patients (58.6% female) with a median age of 36.90 (26.35-49.35) years who were hospitalized for 17 (12-25) days, in which 5.4% mortality occurred. Overall COVID-19 patients were dominated by non-Papuan race (75%). The most frequent comorbidities were hypertension (19.1%), electrolyte imbalance (10.2%), and diabetes (10.0%). Increased mortality rates were significantly associated with older age (≥65 years), cerebrovascular conditions, hypertension, coronary heart disease, liver disease, diabetes, and electrolyte imbalance (P<0.05). Moreover, several comorbidities, such as hypertension, coronary heart disease, diabetes and electrolyte imbalance, and a principal diagnosis of critical COVID-19, were associated with a significantly shorter period of LOS (P<0.05).

Conclusion: Mortality and LOS due to COVID-19 in RSUD Abepura, Papua, are influenced by older age and several comorbidities.

Keywords: comorbidity, coronavirus, COVID-19, length of stay, mortality, SARS-COV-2

Corresponding Author:
Yenny Belinda Jioe | Department of Pulmonology and Respiratory Medicine, Abepura Regional General Hospital, Papua, Indonesia | yennybelinda@gmail.com

Submitted: September 2nd, 2022
Accepted: October 18th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 298–310
https://doi.org/10.36497/jri.v42i4.375

INTRODUCTION

The formerly named "2019 novel coronavirus" (2019-nCoV), which was initially identified in Wuhan, China, in December 2019, spread rapidly worldwide and became a pandemic by January 2020 when the World Health Organization (WHO) declared a global health emergency towards it.[1,2] On February 11, 2020, WHO issued the official name of the 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2), which manifested as COVID-19. The clinical manifestations of COVID-19 range from a mild flu-like illness to severe acute respiratory distress syndrome (ARDS) and multi-organ failure.[2–4]

As of March 5, 2021, there were 115,289,961 confirmed cases of COVID-19 in 222 countries, which were responsible for 2,564,560 deaths (case fatality rate/CFR of 2.2%) globally. Indonesia was responsible for 1,368,069 confirmed COVID-19 cases with 37,026 deaths (CFR 2.7%). Moreover, at the beginning of July 2021, new cases surged to 2,313,829 cases, and 61,140 deaths were reported.[5] However, the scarcity of tracking and tracing in Indonesia's COVID-19 management system resulted in an enormous underreporting of COVID-19 cases.

Besides affecting people's health, COVID-19 has severely affected Indonesia's economic stability. An analysis involving more than 12,000 representative households across all 34 provinces in Indonesia held by UNICEF in May 2021 revealed that 74.3% of the participants experienced decreased earnings due to the unprecedented pandemic. The study also concluded that one in ten people in Indonesia lives below the national poverty line.[6] This

problem is even more evident in Papua, the country's most underdeveloped and impoverished area.[7]

In order to solve the burden of COVID-19, treating this highly contagious infection requires proper medical management, medication, and diagnostic equipment. However, these facilities are not always accessible in rural areas such as Papua. Limited diagnostic centers and capacity, challenging geographical conditions, and transportation costs hinder adequate COVID-19 management in Papua. The limitation of decent health facilities and low resources in Papua also contributes to undetected chronic comorbidities and worsens COVID-19 outcomes.[8]

In addition to those limitations, the COVID-19 pandemic has increased the healthcare system burden as Papua has long struggled with controlling various infectious diseases. According to the Health Ministry Annual Report, Papua has 86,022 active cases of malaria (2021), approximately 842,000 cases of tuberculosis (2017), and 3,753 cases of HIV (2019).[9–11] Additionally, non-infectious diseases (cardiovascular disease, chronic pulmonary disease, diabetes, and others) accounted for 73% of mortality.[12] Related to the COVID-19 pandemic, there is no current scientific report on COVID-19 research in Papua. Thus, this study aims to report the demographics, clinical manifestations, and comorbidities of COVID-19 patients from March 2020 to March 2021 in Abepura Regional General Hospital, Papua.

METHODS

In this retrospective cohort study, we observed and analyzed COVID-19 patients admitted to Abepura Regional General Hospital (RSUD Abepura), Papua, Indonesia, between March 2020 and March 2021. We conducted a descriptive and analytical study focusing on the association of clinical profile (demographic, comorbidities, and diagnoses) with mortality and length of stay (LOS). The diagnoses of COVID-19 complied with Indonesia's national COVID-19 guidelines during the study period.[13] We included all patients who were hospitalized due to COVID-19 with the following criteria: 1) asymptomatic or symptomatic patients who tested positive for SARS-COV-2 reverse transcription polymerase chain reaction (RT-PCR) (first RT-PCR and/or second RT-PCR), or 2) symptomatic patients (presenting with upper respiratory or pneumonia manifestations) who tested positive for SARS-COV-2 rapid antigen. However, we excluded suspected/probable COVID-19 patients who tested negative in two consecutive RT-PCR.

Data such as age, sex, race, comorbidities, admitting and principal diagnoses (i.e., mild, moderate, severe, and critically ill), length of stay (LOS), and outcomes (discharged or deceased), were obtained from medical records and recorded using Microsoft Excel (Microsoft, USA) by the research team. Patient ID was recorded as initials to ensure anonymity; comorbidities were obtained from history taking, physical examination, laboratory, and radiology tests; admitting diagnoses were recorded at admission by doctors on duty; the attending pulmonologist established principal diagnoses; length of stay was calculated from the admission day until deceased/discharged. The ethical clearance for this study was exempted by the Medical and Ethics Committee of Abepura Regional General Hospital (RSUD Abepura), Papua, Indonesia.

Descriptive statistics included frequencies and percentages for each categorical data. We presented normally distributed numerical data in mean±SD, while median and interquartile range (IQR) to present skewed numerical data. The descriptive study was explained in tables and graphs. Analytical statistics included a normality test followed by a comparison/association test. When the Kolmogorov-Smirnov normality test showed a skewed distribution, we utilized Mann-Whitney or Kruskal-Wallis test (followed by a post hoc test with Bonferroni correction when necessary) to analyze the association between independent variables (age, sex, race, comorbidities, admitting and principal diagnoses) and LOS. We used the t-independent or ANOVA test when the data showed normal distribution. We used the Chi-square test to analyze the association between independent variables with mortality when the independent

variables consisted of two groups; otherwise, Fisher's exact test was used. Moreover, the significance value was set to *P*<0.05. All analyses were conducted in IBM SPSS.

RESULTS

A total of 461 patients comprising 270 females (58.6%) and 191 males (49.4%) with a median age of 36.90 years old (IQR 26.35-49.35) were included in this study (Figure 1). According to the age group (Figure 1), most of the included patients were between 19 and 44 years old (60.5%), followed by the age group of 45 to 64 years old (28.0%), 0 to 18 years old (6.5%) and ≥65 years old (5.0%). Regarding race, we recorded that overall COVID-19 patients were dominated by non-Papuan (75%) than Papuan (25%).

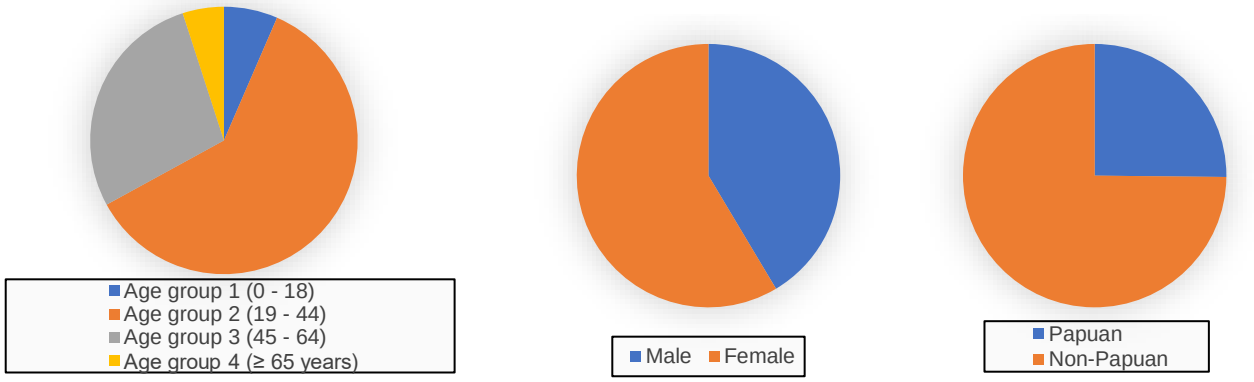

Figure 1. Proportion of COVID-19 patients based on age group (A), sex (B), and race/ethnicity (C)

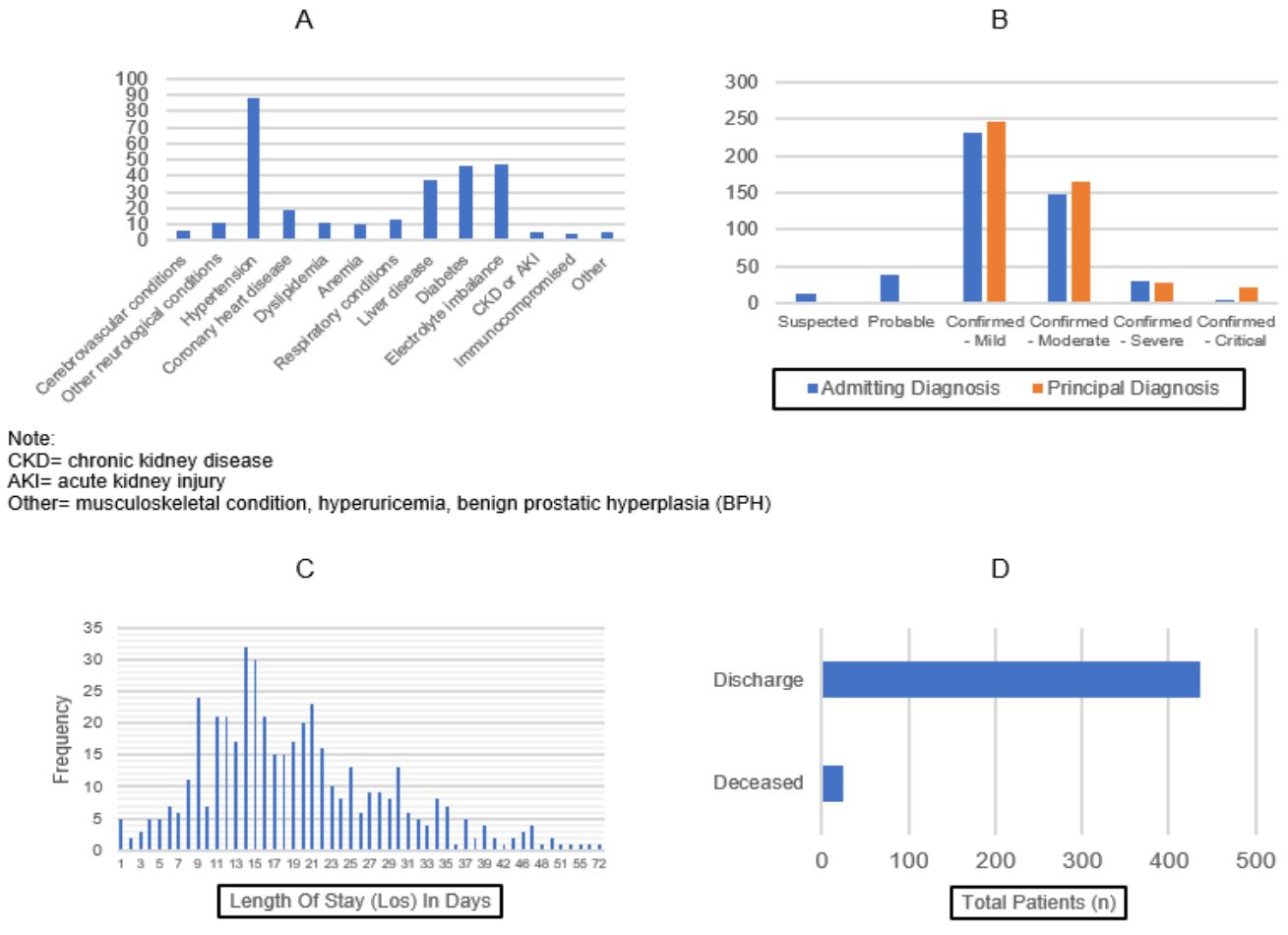

Figure 2. The proportion of pre-existing comorbidities (A), admitting and principal diagnoses (B), length of stay (C), and outcomes in COVID-19 patients.

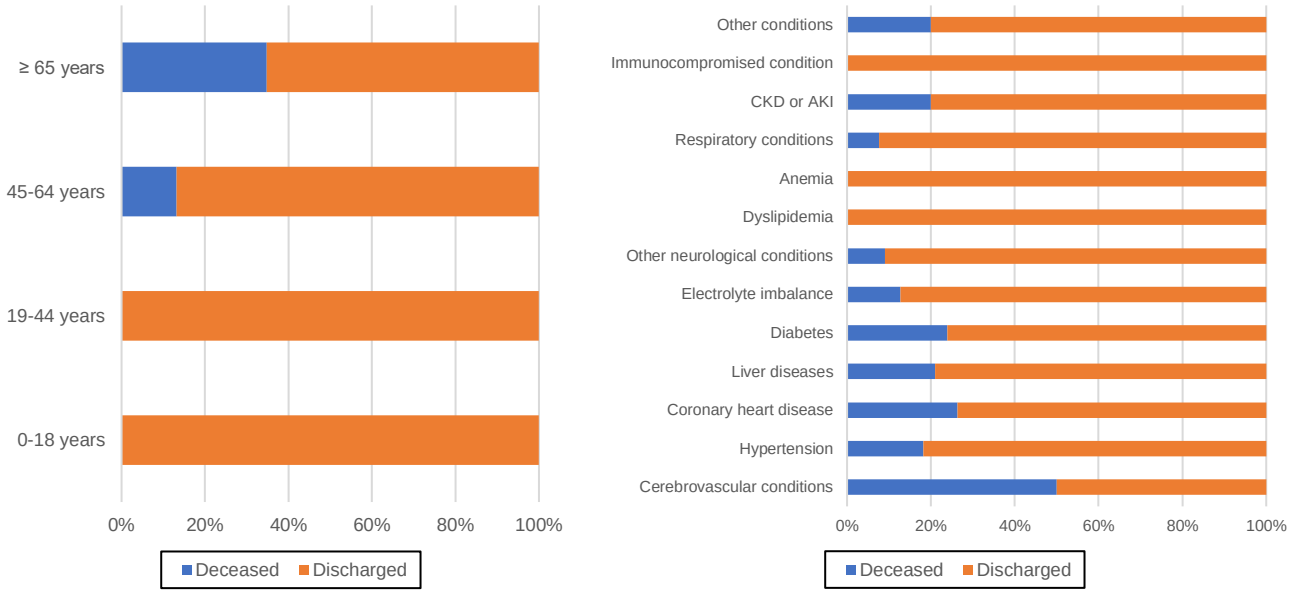

Fig. 3. The outcomes of hospitalized COVID-19 patients based on age groups (A) and comorbidities (B).

Figure 2 shows that the most prevalent comorbidities were hypertension, electrolyte imbalance, and diabetes. Most patients (231/50.1%) were diagnosed with confirmed COVID-19 with mild manifestation at admission. However, after a complete examination, the study revealed that 53.6% of the patients were diagnosed with mild manifestation, 32.1% were moderate, 6.1% were severe, and 4.6% were critically ill (Table 1). These patients were hospitalized for a median of 17 days (IQR=12-25), ranging from 1 to 72 days (Figure 2), in which 25 deaths occurred (mortality rate 5.4%). Moreover, Figure 3 demonstrates that deceased cases were higher among the ≥65 years old group and patients with cerebrovascular conditions.

Table 1 presents the association between all independent variables (age, sex, race, comorbidities, admitting, and principal diagnoses) with mortality and LOS. Our analyses showed that all deceased patients were ≥45 years old, with patients ≥65 years old having a significantly higher risk of mortality compared to <65 years old (OR=13.21 [95% CI=4.93-35.39], *P*=0.0001). Moreover, a significant increase of mortality was found in patients presenting with cerebrovascular conditions (OR=19.68 [95% CI=3.76-103.17], *P*=0.003), hypertension (OR=8.99 [95% CI=3.82-21.13], *P*=0.0001), coronary heart disease (OR=7.54 [95% CI=2.47-22.99], *P*=0.002), liver disease OR=6.37 [95% CI=2.54-15.96], *P*=0.0001), diabetes (OR=9.00 [95% CI=3.80-21.32], *P*=0.0001), and electrolyte imbalance (OR=3.04 [95% CI=1.12-8.05], *P*=0.032). However, we could not analyze the association between admitting and principal diagnoses with mortality due to the small sample size for logistic regression.

As for the LOS, we found that Papuan patients have a significantly shorter LOS than non-Papuan (a median of 15 days vs. 18 days, *P*=0.007). Similarly, the patients with cerebrovascular conditions had a significantly shorter LOS than those without cerebrovascular conditions (a median of 9 days vs. 18 days, respectively, *P*=0.021). However, our further analyses demonstrated no significant LOS difference between deceased and discharged patients who presented with cerebrovascular conditions (Table 2).

In contrast, among COVID-19 patients with hypertension (a median of 3.50 days vs. 20.50 days), coronary heart disease (a mean of 8.40 days vs. 24.43 days), diabetes (a mean of 4.73 days vs. 21.94 days), and electrolyte imbalance (a median of 8 days vs. 19 days) exhibited significantly shorter LOS in deceased patients. Likewise, patients with a principal diagnosis of critical COVID-19 were hospitalized for a significantly shorter LOS than those with mild, moderate, and severe COVID-19 (*P*=0.0001, *P*=0.0001, *P*=0.024). Other independent variables showed no significant differences in terms of LOS.

Table 1. Characteristic of demographic, comorbidities, diagnoses, outcomes, and LOS in COVID-19 patients in RSUD Abepura.

Parameter	Total N=461	Discharged (n=436)	Deceased (n=25)				LOS (days)	
			N	*P*	Effect size (Phi)	OR (95% CI)	Median (IQR)	*P*
LOS	17 (12-25)							
Age	36.90 (26.35-49.35)							
Age group								
0-18 years	30 (6.5%)	30 (6.5%)	0 (0,0%)	0.0001*[g]	0.297[g]	13.21 (4.93-35.39)[g]	15 (11-22)	0.193[a]
19-44 years	279 (60.5%)	279 (60.5%)	0 (0,0%)				18 (14-25)	
45-64 years	129 (28.0%)	112 (24.3%)	17 (3.7%)				18 (12-24.5)	
≥65 years	23 (5.0%)	15 (3.3%)	8 (1.7%)				13 (6-25)	
Sex								
Male	191 (41.4%)	177 (38.4%)	14 (3.0%)	0.128[b]	0.071	1.86 (0.83-4.20)	16 (12-24)	0.314
Female	270 (58.6%)	259 (56.2%)	11 (2.4%)				18 (13-26.25)	
Race								
Papuan	116 (25%)	106 (22.8%)	10 (2.2%)	0.079[b]	0.082	0.482 (0.210-1.104)	15 (12-21)	0.007†*
Non-Papuan	345 (75%)	330 (71.8%)	15 (3.2%)				18 (13-27)	
Comorbidity								
Cerebrovascular conditions (Ischemic stroke and hemorrhagic troke)								
Present	6 (1.4%)	3 (0.7%)	3 (0.7%)	0.003*	0.226	19.68 (3.76-103.17)	9 (1.75-16.75)	0.021*
Absent	455 (98.6%)	433 (93.9%)	22 (4.7%)				18 (13-25)	
Other neurological conditions (Tuberculoma, toxoplasmosis, cephalgia, and SOL)								
Present	11 (2.4%)	10 (2.2%)	1 (0.2%)	0.462	0.025	1.78 (0.22-14.44)	16 (9-24)	0.488
Absent	450 (97.6%)	426 (92.4%)	24 (5.2%)				17 (12-25)	
Hypertension								
Present	88 (19.1%)	72 (15.6%)	16 (3.5%)	0.0001*	0.274	8.99 (3.82-21.13)	20 (11.25-23)	0.949
Absent	373 (80.9%)	364 (79.0%)	9 (2.0%)				17 (12.5-25)	
Coronary heart disease								
Present	19 (4.1%)	14 (3.0%)	5 (1.1%)	0.002*	0.191	7.54 (2.47-22.99)	13 (8.25-22.50)	0.103
Absent	442 (95.9%)	422 (91.5%)	20 (4.3%)				18 (13-25)	
Diabetes								
Present	46 (10.0%)	35 (7.6%)	11 (2.4%)	0.0001*	0.272	9.00 (3.80-21.32)	17 (9-23.25)	0.298
Absent	415 (90.0%)	401 (87.0%)	14 (3.0%)				17 (13-25)	
Dyslipidemia								
Present	11 (2.4%)	11 (2.4%)	0 (0,0%)	1.000	0.037	1.06 (1.04-1.08)	21 (17-28)	0.278
Absent	450 (97.6%)	425 (92.2%)	25 (5.4%)				17 (12-25)	
Anemia								
Present	10 (2.2%)	10 (2.2%)	0 (0,0%)	1.000	0.036	1.06 (1.04-1.08)	15 (12.5-17)	0.149
Absent	451 (97.8%)	426 (92.4%)	25 (5.4%)				18 (12-25)	
Respiratory conditions (Pulmonary tuberculosis, asthma, and COPD)								
Present	13 (2.8%)	12 (2.6%)	1 (0.2%)	0.520	0.017	1.47 (0.18-11.80)	22 (13-34.5)	0.264
Absent	448 (97.2%)	424 (92.0%)	24 (5.2%)				17 (12-25)	
Liver disease (Hepatitis B or C, cirrhosis, and unexplained elevated liver enzyme)								
Present	38 (8.2%)	30 (6.5%)	8 (1.7%)	0.0001*	0.207	6.37 (2.54-15.96)	19 (13.5-25.25)	0.540
Absent	423 (91.8%)	406 (88.1%)	17 (3.7%)				17 (12-25)	
Electrolyte imbalance								
Present	47 (10.2%)	41 (8.9%)	6 (1.3%)	0.032*	0.109	3.04 (1.12-8.05)	18 (12-21)	0.555
Absent	414 (89.9%)	395 (85.7%)	19 (4.1%)				17 (12-25)	
CKD or AKI								
Present	5 (1.1%)	4 (0.9%)	1 (0.2%)	0.244	0.067	4.5 (0.48-41.83)	23 (10.5-25.5)	0.894
Absent	456 (98.9%)	432 (93.7%)	24 (5.2%)				17 (12-25)	
Immunocompromised condition (HIV/AIDS or cancer)								
Present	4 (0.9%)	4 (0.9%)	0 (0,0%)	1.000	0.022	1.06 (1.04-1.08)	21.5 (12-41.5)	0.532
Absent	457 (99.1%)	432 (93.7%)	25 (5.4%)				17 (12-25)	
Other (Musculoskeletal condition, hyperuricemia, benign prostatic hyperplasia)								
Present	5 (1.1%)	4 (0.9%)	1 (0.2%)	0.244	0.067	4.5 (0.48-41.83)	18 (11.5-26)	0.981
Absent	456 (98.9%)	432 (93.7%)	24 (5.2%)				17 (12-25)	

Parameter	Total N=461	Discharged (n=436)	Deceased (n=25)				LOS (days)	
			N	*P*	Effect size (Phi)	OR (95% CI)	Median (IQR)	*P*
Admitting Diagnosis								
Suspected	12 (2.6%)	12 (2.6%)	0 (0,0%)				13 (8.25-18.75)	
Probable	39 (8.5%)	29 (6.3%)	10 (2.2%)				15 (11-24)	
Confirmed Mild	231 (50.1%)	231 (50.1%)	0 (0,0%)		N/A[h]		17 (13-27)	0.004[a,f]
Confirmed Moderate	148 (32.1%)	147 (31.9%)	1 (0.2%)				19 (14-23.75)	
Confirmed Severe	30 (6.5%)	17 (3.7%)	13 (2.8%)				14 (6.75-21)	
Confirmed Critical	1 (0.2%)	0 (0,0%)	1 (0.2%)				-	
Principal Diagnosis								
Confirmed Mild	247 (53.6%)	247 (53.6%)	0 (0,0%)				17 (13-27)[c]	
Confirmed Moderate	165 (35.8%)	165 (35.8%)	0 (0,0%)		N/A[h]		19 (14-23.5)[d]	0.0001[a]*
Confirmed Severe	28 (6.1%)	22 (4.8%)	6 (1.3%)				15.5 (9.5-23)[e]	
Confirmed Critical	21 (4.6%)	2 (0.4%)	19 (4.1%)				5 (2.5-14.5)[c,d,e]	

Note= *Statistically significant (*P*<0.05); [†]Analyzed with Mann-Whitney test; [an]Analyzed with Kruskal-Wallis test; [b]Analyzed with Chi-square; [c]Post hoc test showed a significant difference (*P*=0.0001); [d] Post hoc test showed a significant difference (*P*=0.0001); [e]Post hoc test showed a significant difference (*P*=0.024); [f] False-positive significance due to multiple comparison tests (post hoc test showed insignificant difference); [g]Comparison was between ≥65 years old and <65 years old; [h]Logistic regression test could not be performed due to the small sample size; N/A=data not available

Table 2. The association between the outcome in COVID-19 patients presenting with comorbidities with LOS

Comorbidities (n)	LOS (mean±SD or median (IQR))	*P*
Cerebrovascular conditions		
Deceased (3)	4.67±5.51	0.207[a]
Discharged (3)	16.67±12.66	
Hypertension		
Deceased (16)	3.50 (1.25-11)	<0.001*[b]
Discharged (72)	20.50 (16.25-24.75)	
Coronary heart disease		
Deceased (5)	8.40±10.14	0.021*[a]
Discharged (14)	24.43±12.58	
Liver diseases		
Deceased (8)	15 (6-24)	0.195[b]
Discharged (30)	19 (14-26.5)	
Diabetes		
Deceased (11)	4.73±3.58	<0.001*[a]
Discharged (35)	21.94±10.11	
Electrolyte imbalance		
Deceased (6)	8 (3.75-18.75)	0.029*[b]
Discharged (41)	19 (13-22)	
Other neurological conditions		
Deceased (1)	9.00	N/A[c]
Discharged (10)	18.90±10.87	
Dyslipidemia		
Deceased (0)	N/A[c]	N/A[c]
Discharged (11)	20.91±7.04	
Anemia		
Deceased (0)	N/A[c]	N/A[c]
Discharged (10)	14.60±3.20	
Respiratory conditions		
Deceased (1)	1.00	N/A[c]
Discharged (12)	25.75±14.25	
CKD or AKI		
Deceased (1)	12.00	N/A[c]
Discharged (4)	20.75±8.18	
Immunocompromised condition		
Deceased (0)	N/A[c]	N/A[c]
Discharged (4)	25.00±15.77	
Other		
Deceased (1)	11.00	N/A[c]
Discharged (4)	20.50±6.81	

Note: *Statistically significant (p<0.05); [an]Analyzed using a T-independent test; [b]Analyzed using Mann-Whitney;[c]Statistic test could not be performed due to the small sample size; N/A=data not available; CKD=chronic kidney disease; AKI=Acute kidney injury

DISCUSSION

Our study revealed that most confirmed COVID-19 cases in RSUD Abepura, Papua, from March 2020 to March 2021, were among young adults and the middle age group (19 to 44 years old) at about 61% of total cases. A previous epidemiological study in Jakarta also demonstrated that patients aged 20 to 49 dominated the COVID-19 cases with a proportion of 51.2%, followed by the 50 to 59 years old group (37.6%).[14]

Regarding patients' sex, we found more female patients than males in our study (59% vs. 41%, respectively). Several studies reported the COVID-19 incidence varied; some found the COVID-19 incidence was higher among males,[15,16,] while other studies found that females were counted higher.[17,18] However, there are similarities in multiple studies that show males are prone to progress into severe conditions.[16,19]

A study by Biswas et al showed that males were prone to SARS-COV-2 infection and associated with a significantly increased mortality risk than females because of the higher expression of angiotensin-converting enzyme 2 (ACE-2) in males.[20] In addition, Ciarambino et al found that males tend to have two times higher risk of mortality as androgen hormones (testosterone) were associated with immunosuppressive effects and reduced cellular immune activation.[21,22] On the contrary, estrogen plays a role in immune stimulation and responses, such as managing cytokines activity (IL-1, IL-10, and interferon-gamma).[21]

Moreover, our study also recorded two different races of COVID-19 patients in RSUD Abepura. The dominating race, non-Papuan patients, accounted for three-fold higher than Papuan (indigenous or mixed) patients. We assume that Papuan tend to settle in their homeland for living and working purposes rather than moving to other cities. Most non-Papuans travel for business from Papua to their residential city, particularly in the annual or "Hari Raya" exodus. Interestingly, the unequal distribution of COVID-19 testing in rural Indonesia occurs as moderate to low-income residents cannot afford it. Thus, it may be that many undiscovered cases of COVID-19 in Papua.

We recorded the overall mortality rate of 5.4% and compared it between the age group of ≥65 years old and <65 years old, which showed that the age group of ≥65 was associated with a higher mortality rate (Table 1). A research article by Hazeldine and Lord explained that the physiological aging of the immune system, occurring as rising C-reactive protein (CRP) levels and some pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-8), is associated with a chronically increased basal inflammation in healthy elderly that contributes to increased lung inflammation susceptibility.[21,23] The downregulation of the innate immune system in the elderly, such as phagocytosis, antigen-presenting process, and bactericidal activity, leads to extensive inflammation and tissue injury in severe SARS-COV-2 infection.[23,24]

The deceased case in our study was reported to be higher in non-Papuan patients, but it showed no difference between those two races regarding mortality. There was limited research on Indonesia's race and ethnicity towards COVID-19. However, some studies elucidated several factors that associated race and ethnicity with mortality, such as culture, behaviors, and socioeconomic status.[25] Another systematic review in the USA found that worse outcome of race and ethnicity-related COVID-19 was associated with lower socioeconomic status and poverty, which increased difficulty in accessing medical care (diagnostic testing and treatment); hence those factors contributed to higher mortality rates.[26]

Our study showed that cerebrovascular conditions (cerebral infarction or hemorrhagic stroke) constituted the most prominent comorbidity associated with mortality. The mortality risk in patients with cerebrovascular conditions was around 19 times higher than in COVID-19 patients without this comorbidity. Hypoxia in the central nervous system due to impairment of the alveolar gas exchange leads to cerebral insufficiency. As a result of hypoxia, anaerobic metabolism activation will produce acid metabolites. Then, the accumulation of

acid metabolites impacts cerebral adverse events, such as cells and interstitial edema, as well as blood flow impairment, worsened by cytokine cascades and coagulopathy during SARS-COV-2 infection triggering the acute cerebrovascular disease.[27] Through this mechanism, COVID-19 patients with cerebrovascular comorbidity, may exacerbate cerebral infarction or intracranial bleeding.[28] Thus, the incidence of severe infection and mortality is higher in this population.

Furthermore, hypertension remained the most significant proportion of comorbidities and was related to mortality in SARS-CoV-2 infection. The prevalence of hypertension was higher among older age with diabetes and kidney disease.[29] Rozaliyani et al reported that hypertension is the most frequent comorbidity of lethal outcomes among patients. They reported diabetes and heart disease as the second most common pre-existing condition among COVID-19 patients.[14]

Likewise, our study recorded hypertension (19.1%) as the most significant proportion of comorbidities among COVID-19 patients, followed by electrolyte imbalance (10.2%), diabetes (10%), liver disease (8.2%) and coronary heart disease (4.1%). Patients with hypertension were significantly associated with mortality, showing a nine-time higher mortality risk. Likewise, a previous study by Pranata et al demonstrated that hypertension comorbidity resulted in lethal outcomes.[30]

Previous studies also explained that hypertensive patients would be more severely affected by COVID-19 because of ACE-2.[30–32.] The virus is capable of binding the ACE-2 receptor on the lung epithelial cell. Hence, this binding negatively impacts the activity of ACE-2 to neutralize the inflammatory effect of angiotensin II and induce antioxidant roles of angiotensin 1-7.[30] The downregulation of ACE-2 simultaneously occurs with angiotensin II activation through type 1 receptors (ATR1) which caused dysregulation of the renin-angiotensin-aldosterone system (RAAS). Furthermore, it may induce vascular permeability, alveolar damage, pulmonary edema, and ARDS.[32–34]

The pre-existing cardiovascular condition we recorded in our study was coronary heart disease (CHD), demonstrating a strong association with mortality at around seven times more than patients without CHD. Kang et al found that COVID-19 patients with cardiovascular comorbidity had a higher tendency to have a cardiac injury than patients without cardiovascular comorbidity. The ACE-2 expression in human myocardial cells explains SARS-COV-2 infection-induced myocardial damage by several events, such as a hyperinflammation state that progresses to vascular inflammation, myocardial injury, unstable plaque, and hyper-coagulability.[35] In addition, heart damage worsened because of the imbalance between the demand and supply of oxygen to myocardial cells due to systemic consequences of COVID-19.[36]

Type 2 diabetes (T2D) was another pre-existing condition related to mortality (Table 1). In a previous study, diabetes was one of the cardiovascular risk factors that related to the severity and poor outcome in COVID-19 patients.[37] This finding is expected because diabetic patients have higher pro-inflammatory states, RAAS activity, vascular dysfunction, and prothrombotic condition prior to SARS-COV-2 infection. Besides, the immune imbalance in T2D patients, including elevated inflammatory markers (e.g., neutrophil, IL-6, and CRP) and delayed response and recruitment of CD4+ T cells, influence several detrimental outcomes.[38]

Furthermore, SARS-COV-2 infection in the T2D population induces direct beta cell destruction in pancreatic islets that impairs insulin production; therefore, the destruction of beta cells contributes to an over-inflammation state by releasing IL-1β and TNF-α that worsen systemic insulin resistance. Hence, type 2 diabetes patients, particularly among uncontrolled blood glucose T2D, tend to develop severe manifestations, complications (e.g., ARDS, septic shock, and disseminated intravascular coagulation/DIC) as well as higher mortality risk due to COVID-19.[38,39]

The mortality risk was also associated with the liver disease among hospitalized patients, including viral hepatitis and increased liver enzymes. A study

by Sharma et al supported our findings that patients with elevated AST and ALT were 3-fold and 2-fold at risk of adverse outcomes. Elevated AST and ALT levels indicate liver damage due to direct hepatotoxic injury caused by SARS-COV-2 infection in the biliary epithelium, which also expresses the ACE-2 receptor.[40]

According to Weber et al, patients with a high level of AST and ALT during hospital admission were strongly associated with ICU admission and mechanical ventilator utilization.[41] Moreover, the poor outcome in patients with liver disease is a consequence of direct hepatocytes or cholangiocytes damage through ACE-2 receptor expression, followed by immune-mediated damage associated with liver injury, which may be resulted in a cytokine storm.[40,42] A study in China reported that some severe COVID-19 cases were also associated with hepatitis B infection.[43]

Electrolyte imbalance was described as increased, or decreased levels of sodium, potassium, and chloride recorded prior to COVID-19 or at patient admission to our hospital. Gastrointestinal symptoms in COVID-19 patients, such as diarrhea and nausea, resulted in electrolyte imbalance.[44] The kidney involvement of fluid and electrolyte imbalance also plays a vital role during SARS-COV-2 infection through several processes, such as decreased kidney perfusion, ischemic tubular damage, and RAAS activation that regulate electrolyte homeostasis.[45]

Again, inappropriate RAAS activation via ACE-2 expression is more likely to induce excessive excretion of electrolytes by the kidneys, contributing to higher mortality in COVID-19 patients with electrolyte imbalance.[44,45] Lippi et al recorded that sodium and potassium levels in severe COVID-19 were significantly lower than in non-severe COVID-19, particularly hypokalemia, which may worsen ARDS and cardiac injury.[46]

Our descriptive study showed that the overall median (IQR) LOS was 17 days (12-25 days). Most cases in our study manifested as mild-moderate clinical symptoms on both the admitting and principal diagnoses. Several factors influenced the prolonged hospitalization in this clinical manifestation group, such as 1) limited diagnostic tools in performing PCR tests, which nasopharyngeal/oropharyngeal swab samples should be examined in Jakarta in the first month of the pandemic, and 2) more extended time to acquire two consecutive negative PCR results, even though patients showed clinical improvement. Severe-critical manifestations exhibited less than 10% of overall positive cases and a shorter period of LOS. Rees et al found a shorter period of LOS among deceased (4-21 days) than discharged cases (4-53 days).[47]

This supports our finding that all deceased patients were hospitalized with severe-critically ill manifestations (median 15 days and five days, respectively. We assumed severe-critical conditions contributed to a shorter period of hospitalization due to late hospital arrival. Mortality-related shorter hospitalization period in this group was associated with the COVID-19 timeline that most severe-critical ill patients who arrived in the hospital were in the pulmonary phase/inflammatory phase, which exhibited dyspnea onset, bilateral pulmonary infiltrates, and ARDS progression. In this regard, patients showed life-threatening conditions, such as multi-organ failure and ARDS, resulting from immune system dysregulation and hypercoagulable condition during the pulmonary phase.[48]

Regarding race, our study found that Papuan patients (15 days) had shorter LOS than non-Papuan patients (18 days). Further observation is essential to discover whether the shorter LOS is associated with poor outcomes or not based on the association of race with other parameters (e.g., demographics, comorbidities, and diagnoses). Regarding comorbidity, patients with cerebrovascular conditions showed a shorter period of hospitalization than those without this comorbidity. We further analyzed the association of COVID-19 outcomes with LOS among patients with comorbidities. Our analyses demonstrated no significant LOS difference between deceased and discharged cerebrovascular-conditions-presenting patients (Table 2).

In contrast, other comorbidities, such as hypertension, coronary heart disease, type 2

diabetes, and electrolyte imbalance, significantly differed in a shorter period of LOS between deceased and fully recovered patients presenting with those comorbidities. In our study, a shorter period of LOS was predicted to be associated with severe illness progression and mortality. Zaenab et al also found that some comorbidities, such as hypertension, diabetes, and cardiovascular disease, were prone to worse outcomes (e.g., respiratory failure and mortality).[49]

LIMITATION

The retrospective cohort study in RSUD Abepura can be the closest reflection of COVID-19 incidence on behalf of the pandemic phenomenon in Papua, Indonesia. However, independent variables should be followed up continually, particularly with small samples and the association of race with other variables, to observe the correlation with COVID-19 outcomes. It is essential to add clinical symptoms to make the diagnoses more precisely analyzed in association with outcomes, which we only summarized as mild, moderate, severe, and critical ill manifestations. Hopefully, this research will proceed to the second year of the COVID-19 pandemic, guided by the national guideline following the pandemic period. Thus, we can observe the COVID-19 pandemic progression in Papua, Indonesia.

CONCLUSION

COVID-19 patients from March 2020 to March 2021 in RSUD Abepura, Jayapura, Papua, are predominantly aged 19 to 44. The higher incidence of mortality was influenced by older age (≥65 years old) and comorbidities. Cerebrovascular conditions, hypertension, diabetes, and cardiovascular disease were the main concerns related to higher mortality associated with SARS-COV-2 infection. In terms of LOS, severe to critical manifestation and deceased cases showed a shorter period of hospitalization. In addition, a shorter period of LOS was also shown among deceased or discharged patients presenting with hypertension, coronary heart disease, type 2 diabetes, and electrolyte imbalance, as those conditions were strongly associated with mortality. Delays in medical treatment and hospitalization may contribute to higher mortality in Jayapura. Accordingly, stakeholders' involvement is crucial to repeatedly promote public awareness of the disease.

ACKNOWLEDGMENTS

We thank the Department of Pulmonology and Respiratory Medicine, Abepura Regional General Hospital (RSUD Abepura), Papua, for continuing support for this study and Wiliam Alexander Matulessy (COVID-19 Surveillance staff of RSUD Abepura, Papua) for assisting the data collection. We also thank Brigita De Vega, MD, MSc (University College London, United Kingdom), for her editing assistance in preparing the manuscript.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924.
2. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71–6.
3. Oda Y, Shiraishi S, Shimada M, Kurai O. Clinical profiles and outcome of patients with COVID-19 in a specialized hospital in Japan. J Anesth. 2021;35(3):405–11.
4. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. 2021 [cited 2021 Aug 24]. Available from:

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

5. World Health Organization Indonesia. WHO Indonesia Situation Report-18 who.int/indonesia Situation Report-7 INDONESIA Situation Report 19 Internal for SEARO [Internet]. 2020 Jul [cited 2022 Jul 19]. Available from: https://infeksiemerging.kemkes.go.id/
6. United Nations Children's Fund (UNICEF). Analysis of the social and economic impacts of COVID-19 on households and strategic policy recommendations for Indonesia [Internet]. 2021 [cited 2021 Jul 10]. Available from: https://www.unicef.org/indonesia/coronavirus/reports/socio-economic-impact-covid-19-households-indonesia
7. Badan Pusat Statistik Provinsi Papua. Profil Kemiskinan di Papua September 2020 [Internet]. 2021 [cited 2021 Jul 10]. Available from: https://papua.bps.go.id/pressrelease/2021/02/15/570/profil-kemiskinan-di-provinsi-papua-september-2020.html#:~:text=Persentase%20penduduk%20miskin%20di%20Papua%20untuk%20daerah%20perkotaan%20mengalami%20peningkatan,50%20persen%20pada%20Maret%202020
8. Samudra RR, Setyonaluri D. Inequitable impact of COVID-19 in Indonesia: evidence and policy response policy report. [Internet]. Jakarta; 2020 [cited 2021 Jul 10]. Available from: https://en.unesco.org/inclusivepolicylab/sites/default/files/analytics/document/2020/9/200825_Policy%20Report_Inequitable%20Impact%20of%20COVID%2019%20in%20Indonesia.pdf
9. Direktorat Pencegahan dan Pengendalian Penyakit Tular Vektor dan Zoonotik Kementerian Kesehatan RI. Sebaran Malaria di Indonesia [Internet]. Kementerian Kesehatan Republik Indonesia. 2021 [cited 2021 Aug 24]. Available from: https://www.malaria.id/kasus
10. Gebhard A, Sonata B, Sahanggamu P, Post E. A case study on the role of the USAID-funded challenge tb project in increasing TB case notification in Indonesia challenge TB case study [Internet]. 2019 [cited 2021 Aug 17]. Available from: https://www.challengetb.org/publications/tools/briefs/Case_Study_FTMP_Indonesia.pdf
11. Ditjen P2P (Sistem Informasi HIV/AIDS dan IMS (SIHA). Infodatin Pusat Data dan Informasi Kementerian Kesehatan RI. 2019.
12. 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.
13. Burhan E, Dwi Susanto A, Nasution SA, Ginanjar E, Wicaksono Pitoyo C, Susilo A, et al. Protokol tatalaksana COVID-19 tim penyusun Perhimpunan Dokter Paru Indonesia (PDPI) Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI) Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia (PAPDI) Perhimpunan Dokter Anestesiologi dan Terapi Intensif Indonesia (PERDATIN) Ikatan Dokter Anak Indonesia (IDAI). 2020.
14. Rozaliyani A, Savitri AI, Setianingrum F, Shelly TN, Ratnasari V, Kuswindarti R, et al. Factors associated with death in covid-19 patients in Jakarta, Indonesia: An epidemiological study. Acta Med Indones. 2020;52(3):246–54.
15. Abate BB, Kassie AM, Kassaw MW, Aragie TG, Masresha SA. Sex difference in coronavirus disease (COVID-19): A systematic review and meta-analysis. Vol. 10, BMJ Open. BMJ Publishing Group; 2020.
16. Galbadage T, Peterson BM, Awada J, Buck AS, Ramirez DA, Wilson J, et al. Systematic review and meta-analysis of sex-specific COVID-19 clinical outcomes. Vol. 7, Frontiers in Medicine. Frontiers Media SA; 2020.
17. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;133(9):1025–31.

18. 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).
19. Papadopoulos V, Li L, Samplaski M. Why does COVID-19 kill more elderly men than women? Is there a role for testosterone? Andrology. 2021;9(1):65–72.
20. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of sex, age, and comorbidities with mortality in covid-19 patients: A systematic review and meta-analysis. Vol. 64, Intervirology. S. Karger AG; 2021. p. 36–47.
21. Ciarambino T, Para O, Giordano M. Immune system and COVID-19 by sex differences and age. Vol. 17, Women's Health. SAGE Publications Ltd; 2021.
22. Lanser L, Burkert FR, Thommes L, Egger A, Hoermann G, Kaser S, et al. Testosterone deficiency is a risk factor for severe COVID-19. Front Endocrinol (Lausanne). 2021;12.
23. Hazeldine J, Lord JM. Immunesenescence: A predisposing risk factor for the development of COVID-19? Vol. 11, Frontiers in Immunology. Frontiers Media SA; 2020.
24. Haynes L. Aging of the immune system: research challenges to enhance the health span of older adults. Frontiers in Aging. 2020;1.
25. Pan D, Sze S, Minhas JS, Bangash MN, Pareek N, Divall P, et al. The impact of ethnicity on clinical outcomes in COVID-19: A systematic review. eClinicalMedicine. 2020;23.
26. Magesh S, John D, Li WT, Li Y, Mattingly-App A, Jain S, et al. Disparities in COVID-19 outcomes by race, ethnicity, and socioeconomic status: A systematic-review and meta-analysis. Vol. 4, JAMA Network Open. American Medical Association; 2021.
27. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Vol. 87, Brain, Behavior, and Immunity. Academic Press Inc.; 2020. p. 18–22.
28. Fraiman P, Godeiro Junior C, Moro E, Cavallieri F, Zedde M. COVID-19 and cerebrovascular diseases: A systematic review and perspectives for stroke management. Vol. 11, Frontiers in Neurology. Frontiers Media SA; 2020.
29. Tadic M, Cuspidi C, Mancia G, Dell'Oro R, Grassi G. COVID-19, hypertension and cardiovascular diseases: Should we change the therapy? Vol. 158, Pharmacological Research. Academic Press; 2020.
30. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. JRAAS - Journal of the Renin-Angiotensin-Aldosterone System. 2020;21(2).
31. Ramos SG, Rattis BA da C, Ottaviani G, Celes MRN, Dias EP. ACE2 down-regulation may act as a transient molecular disease causing RAAS dysregulation and tissue damage in the microcirculatory environment among COVID-19 patients. Vol. 191, American Journal of Pathology. Elsevier Inc.; 2021. p. 1154–64.
32. Pagliaro P, Penna C. ACE/ACE2 Ratio: A Key Also in 2019 Coronavirus Disease (Covid-19)? Vol. 7, Frontiers in Medicine. Frontiers Media S.A.; 2020.
33. John Fountain AH, Lappin Affiliations SL. Physiology, renin angiotensin system [Internet]. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470410/?report=printable
34. Simko F, Hrenak J, Adamcova M, Paulis L. Renin–angiotensin–aldosterone system: Friend or foe—the matter of balance. Insight on history, therapeutic implications and COVID-19 interactions. Vol. 22, International Journal of Molecular Sciences. MDPI AG; 2021. p. 1–8.
35. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Vol. 106, Heart. BMJ Publishing Group; 2020. p. 1132–41.

36. Pellicori P, Doolub G, Wong CM, Lee KS, Mangion K, Ahmad M, et al. COVID-19 and its cardiovascular effects: a systematic review of prevalence studies. Vol. 2021, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2021.
37. Kong KA, Jung S, Yu M, Park J, Kang IS. Association between cardiovascular risk factors and the severity of coronavirus disease 2019: Nationwide epidemiological study in Korea. Front Cardiovasc Med. 2021;8.
38. Li G, Chen Z, Lv Z, Li H, Chang D, Lu J. Diabetes Mellitus and COVID-19: Associations and Possible Mechanisms. Vol. 2021, International Journal of Endocrinology. Hindawi Limited; 2021.
39. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020;31(6):1068-1077.e3.
40. Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients – A systematic review and meta-analysis. Ann Hepatol. 2021;21.
41. Weber S, Hellmuth JC, Scherer C, Muenchhoff M, Mayerle J, Gerbes AL. Liver function test abnormalities at hospital admission are associated with severe course of SARS-CoV-2 infection: A prospective cohort study. Gut. 2021;70(10):1925–32.
42. Kumar A, Kumar P, Dungdung A, Kumar Gupta A, Anurag A, Kumar A. Pattern of liver function and clinical profile in COVID-19: A cross-sectional study of 91 patients. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2020;14(6):1951–4.
43. Guan W jie, Liang W hua, Zhao Y, Liang H rui, Chen Z sheng, Li Y min, et al. comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. European Respiratory Journal. 2020;55(5):2000547.
44. Pourfridoni M, Abbasnia SM, Shafaei F, Razaviyan J, Heidari-Soureshjani R. Fluid and electrolyte disturbances in COVID-19 and their complications. Vol. 2021, BioMed Research International. Hindawi Limited; 2021.
45. Nahkuri S, Becker T, Schueller V, Massberg S, Bauer-Mehren A. Prior fluid and electrolyte imbalance is associated with COVID-19 mortality. Communications Medicine. 2021;1(1).
46. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem. 2020;57(3):262–5.
47. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, Carl CA, et al. COVID-19 length of hospital stay: A systematic review and data synthesis. Vol. 18, BMC Medicine. BioMed Central Ltd; 2020.
48. Torres Acosta MA, Singer BD. Pathogenesis of COVID-19-induced ARDS: Implications for an ageing population. European Respiratory Journal. 2020;56(3).
49. Zaenab A, Jose V, Cynthia CJ, Yousuf Z, Claudia M, Hamed S. The effects of comorbidities on COVID-19 patients admitted to the hospital. Fam Med Med Sci Res. 2021;10(2):261.

Original Article

Surfactant Protein A Serum Level in Cement Worker

Gunawan, Sita Laksmi Andarini, Muhammad Ilyas, Arif Santoso, Ahmad Hudoyo, Irawaty Djaharudin, Harun Iskandar, Nur Ahmad Tabri

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine
Universitas Hasanuddin, Makassar, Indonesia

Abstract

Background: Pneumoconiosis occurs almost in entire worldwide. Pneumoconiosis had threatened cement workers. Serologic abnormalities had found in pneumoconiosis. Surfactant Protein A (SP-A) levels increased in silica-exposed workers. Surfactant Protein A (SP-A) may be a helpful biomarker for the early diagnosis of pneumoconiosis, but it has not yet been studied in Indonesia.

Methods: The design of this study was observational with cross-sectional. A sampling of cement-exposed workers was done by consecutive sampling. The subjects were 88, approach population of 67 cement exposed workers from September 2017 – March 2018 and 17 healthy people as control. The serum level of SP-A was measured by the ELISA method. Cement exposed workers is a worker in the production area and workers in the quarry area.

Results: The total number of research subjects met the criteria was 67, and the control subjects were 21. The mean serum SP-A level in the study subject group or the exposed group was 6.02 ng/ml, and the mean SP-A level in the control group was 4.50 ng/ml. The difference in SP-A levels between the exposed and control groups was different but not significant, with value of *P*=0.084.

Conclusion: SP-A levels in the exposed and control groups were different but not statistically significant.

Keywords: Cement workers, Serum surfactant A, Silica exposure

Corresponding Author:
Gunawan | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia| gunawan666un@gmail.com

Submitted: April 21st, 2021
Accepted: August 23rd, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 311-8
https://doi.org/10.36497/jri.v42i4.363

INTRODUCTION

The negative impact of the cement industry is air pollution by dust; the cement industry has the potential to cause air contamination in the form of dust. The dust was produced from procurement of raw materials, combustion process, transportation of raw materials to the factory, and finished materials out of the factory, including their packaging. It should be realized that the development of industrial activities, in general, is also a sector with great potential as a source of air pollution that will be detrimental to health and the environment.[1]

Lung disease caused by harmful dust is called pneumoconiosis. The cement factory is one of the industries that produce dust. An epidemiological study at a cement factory in Tanzania measured levels of dust exposure and found high levels of dust exposure in cranes (38.64 mg/m^3), packing (21.30 mg/m^3), crushers (13.48 mg/m^3), low dust exposure in cement mill (3.23 mg/m^3), kiln (2.87 mg/m^3), raw mill (1.85 mg/m^3), maintenance (1.16 mg/m^3) and administration (0.29 mg/m^3).[2] Based on lung function measurements, 31.6% of respondents had normal lung function, and the remaining 64.4% had impaired lung function. Based on reports of disease patterns from the PT. Semen Tonasa for five years in a row, respiratory disease ranks first.[3]

Data from the World Health Organization (WHO) and The World Labor Organization (ILO) in 2003 reported that about 1.7 million workers were exposed to silica dust. About 10% of workers are at risk of suffering from silicosis in the United States. This finding was also found in Germany, with around 3000 cases of silicosis each year since the 1990s. Furthermore, Japan reports 1,000 new cases yearly, and Australia reports more than 1,000 predicted cases yearly. Every year France reports about 300 new patients diagnosed with silicosis, while China reports 10 million people diagnosed with silicosis, and 5,000 deaths occurred from 1991-1995.[4]

A study found that surfactant A (SP-A) and surfactant D (SP-D) levels increased in patients with Idiopathic Pulmonary Fibrosis (IPF) with Progressive Systemic Sclerosis (PSS).[5] In contrast, Shi Xin et al found that SP-A protein levels were increased in workers exposed to silica. Serum SP-A levels may be used as a biomarker for the early diagnosis of silicosis.[6]

This study aimed to compare the serum SP-A levels of cement factory workers with the average population and the risk factors that affect serum SP-A levels.

METHODS

The research design is a cross-sectional study. This research was conducted at PT. X Pangkep Regency, South Sulawesi Province, and was carried out in September-October 2019. Data collection for control subjects was carried out at the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Hasanuddin University, in November 2019.

The target population is all factory workers at PT. X. The affordable population is the entire target population that works in the raw material and production areas and has worked for five years compared to the control subjects. The control subjects were those who did not work in the cement factory and did not live in the cement factory environment. Samples were taken in September–October 2019.

Sampling was done by consecutive sampling. The subjects studied worked in the raw material area and the production area. The criteria for acceptance of the case subject are factory workers of PT. X in the work area of raw materials and production who has worked for at least five years, male gender, normal BMI, agreed to participate in research, sign approval letters, and take blood samples.

The criteria for acceptance of control subjects were not working in a cement factory, not living in a cement factory environment, did not agree to participate in research and sign a letter of approval, taking blood samples, having normal BMI, and routine chest X-ray.

Respondents' exclusion criteria were refusing to be research subjects, having a history of pulmonary TB, asthma, COPD, and lung tumors.

RESULTS

This study was cross-sectional to determine the difference in serum SP-A levels of cement workers with the normal population. Sampling is done by consecutive sampling. The number of subjects in this study was 67 research subjects and 21 control subjects. Drop-out subjects were two research subjects, 4 study subjects were excluded because of damage to serum labeling.

In this study, SP-A levels were found in the research subject group, the exposed group with an average of 6.02 ng/ml, and the control group with an average of 4.50 ng/ml. Box plot graph describes SP-A levels in the exposed and the control groups. The difference in SP-A levels between the exposed and control groups was different but not significant, with *P*=0.084.

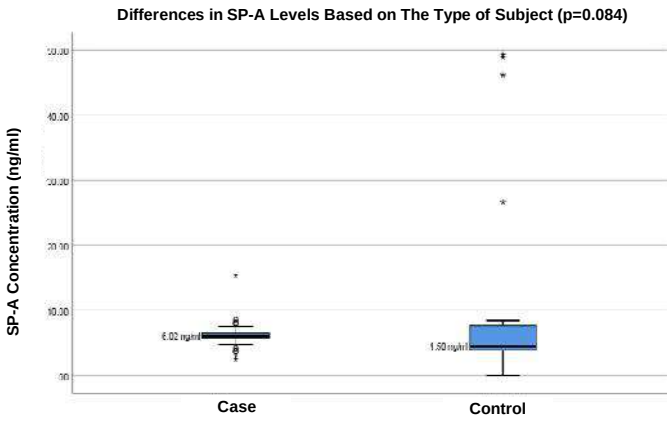

Figure 1. Box plot graphic of serum SP-A levels by age group

Differences in SP-A levels based on respiratory complaints in the exposed group; this study found SP-A levels in two groups, the group with respiratory complaints with an average of 11.97 ng/ml and the group had no respiratory complaints with a mean of 6.02 ng/ml. The difference in SP-A levels between the two groups was significantly different, with *P*=0.017.

Table 1. Characteristics of Research Subjects

Variable	Exposed (n=67)		Control (n=21)		Total (n=88)	
	n	%	n	%	n	%
Gender						
Men	67	100	21	100	88	100
Women	0	0	0	0	0	0
Age						
≥40 years	49	73,1	0	0	49	55,7
<40 years	18	26,9	21	100	39	44,3
Education level						
Low	6	9	0	0	6	6,8
Middle	51	76,1	0	0	51	58
High	10	14,9	21	100	31	35,2
Length of work						
≥10 years	50	74,6	0	0	50	56,8
<10 years	17	25,4	0	0	17	19,3
Smoking history						
Smokers	18	26,9	0	0	18	20,5
Ex-Smokers	7	10,4	0	0	7	8
Non-Smokers	42	62,7	21	100	63	71,6
Brinkman Index						
Mild	12	48	0	0	12	13,6
Moderate	13	52	0	0	13	14,8
Severe	0	0	0	0	0	0
Use of PPE						
Poor	3	4,5	0	0	3	3,4
Moderate	57	85,1	0	0	57	64,8
Good	7	10,4	0	0	7	8
Respiratory complaints						
Exist	2	3	0	0	2	2,3
There is no exist	65	97	21	100	86	97,7
History of inflammation of the respiratory tract						
Exist	2	3	0	0	2	2,3
Did not exist	65	97	0	0	65	73,9
Work Area						
Cement packer	8	11,9	0	0	8	9,1
Kiln	5	7,5	0	0	5	5,7
Crusher	14	20,9	0	0	14	15,9
Finish mill	10	14,9	0	0	10	11,4
Quarry	5	7,5	0	0	5	5,7
Raw mill	8	11,9	0	0	8	9,1
Silica crusher	9	13,4	0	0	9	10,2
Other sites	8	11,9	0	0	8	9,1

Differences in SP-A levels based on a history of respiratory tract inflammation in this study found SP-A levels in two groups, the group with a history of respiratory tract inflammation with an average of 6.51 ng/ml and the group without a history of respiratory tract inflammation with an average of 6.02 ng/ml. The difference in SP-A levels between the two groups showed that the results were not significantly different, with *P*=0.418.

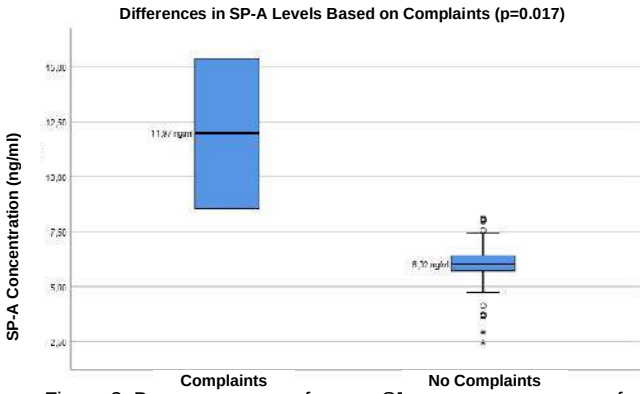

Figure 2. Box plot graphic of serum SP-A levels by a group of respiratory complaints

Differences in SP-A levels based on education level were grouped into low, middle, and high. Groups with low education levels with an average of 6.34 ng/ml, groups with moderate levels of education with an average of 5.96 ng/ml, and groups with high education levels with an average of 5.91 ng/ml. The difference in SP-A levels between the three groups showed that the results were not significantly different, with *P*=0.695.

The difference in SP-A levels based on the length of work in this study found SP-A levels in two groups. The group with an average length of work above ten years with an average of 6.06 ng/ml and a group with an average length of work <10 years with an average of 5.66 ng/ml. The difference in SP-A levels between the two groups of the length of work obtained significantly different results with value of *P*=0.008.

Differences in SP-A levels based on smoking history in this study found SP-A levels in three groups, the smoking group with an average of 6.07 ng/ml, the ex-smoker group with an average of 5.84 ng/ml, and the non-smoker group with an average of 6.01 ng/ml. The difference in SP-A levels between the three smoking history groups showed that the results were not significantly different, with *P*=0.819.

The difference in SP-A levels was based on the Brinkman Index in the three groups. However, there was no sample for severe IB; the group with moderate IB had an average of 5.98 ng/ml, and the group with mild IB had an average of 5.91 ng/ml. The difference in SP-A levels between the two groups based on IB showed that the results were not significantly different, with *P*=0.480.

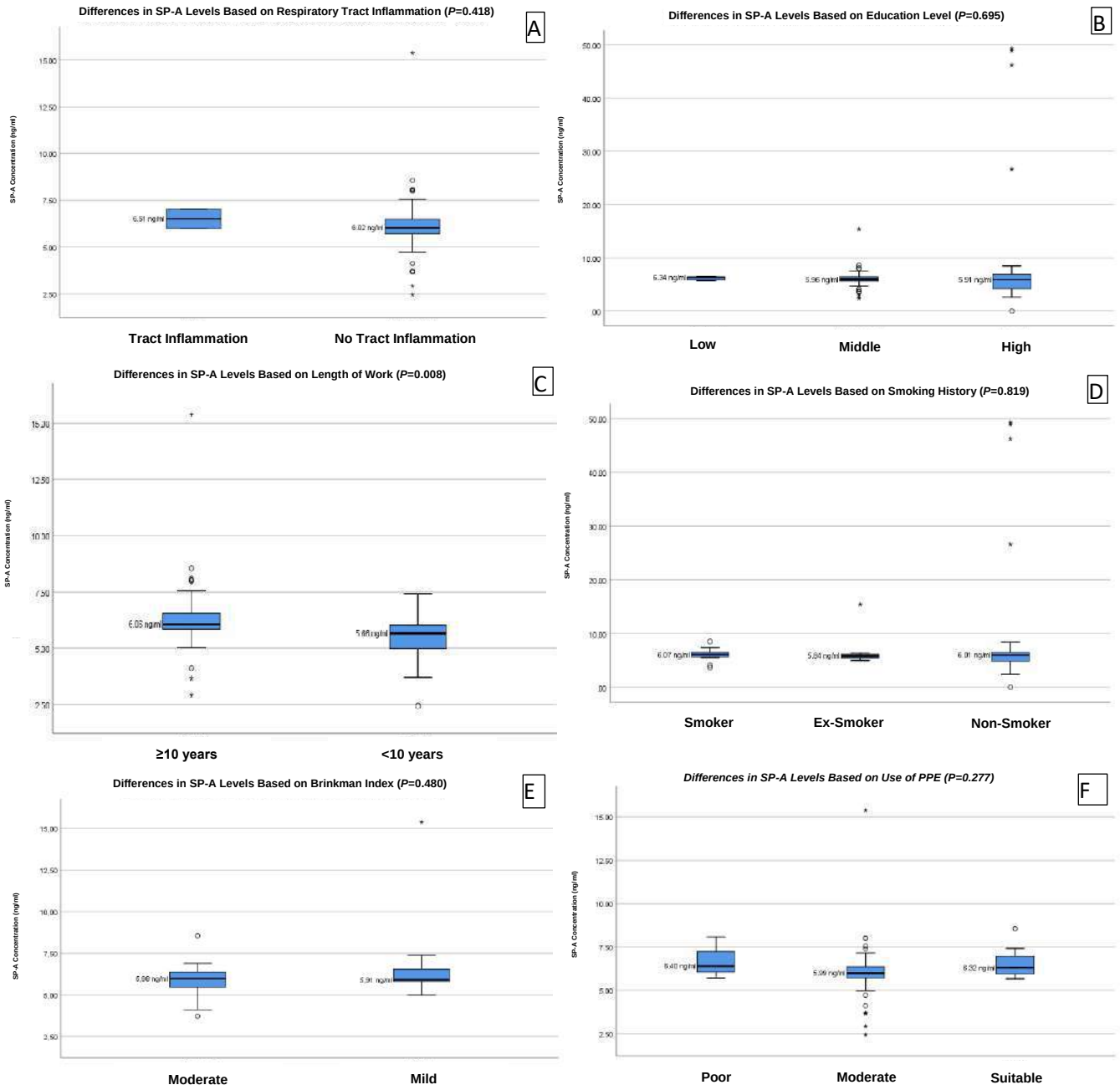

Figure 3. Graphic box plot of serum SP-A levels based on A) history of respiratory tract inflammation in the exposed group; B) education level; C) length of work; D) Smoking History; E) the Brinkman Index; F) use of PPE

Differences in SP-A levels based on the use of PPE, this study found SP-A levels in three groups, the group with poor PPE with an average of 6.40 ng/ml, the group with moderate PPE with an average of 5.99 ng/ml, and the group with suitable PPE with an average of 6.32 ng/ml. The difference in SP-A levels between the three groups using PPE was not significantly different, with *P*=0.277.

Differences in SP-A levels based on the work area with the results of SP-A serum levels in eight groups. The group of cement packer working area with an average of 6.13 ng/ml, the group of kiln working area with an average of 5.82 ng/ml, the group of crusher working area with an average of 6.20 ng/ml, a group of finish mill working area with an average of 5.72 ng/ml, the group of quarry working area with an average of 5.71 ng/ml, the group of raw mill working area with an average of 5.60 ng/ ml, the group of silica crusher working area with an average of 6.37 ng/ml, the group of other working sites with an average of 6.38 ng/ml. The differences in SP-A levels between the eight groups based on the work area were not significantly different.

In this study, the highest dust content was

found in the cement packer area of 31.45 mg/m^3, followed by the crusher area of 9.78 mg/m^3, the finish mill area of 4.41 mg/m^3, and the raw mill area of 0.52 mg/m^3.

Table 2. Total dust content of the working environment by work area

Working Area	Dust Content (mg/m^3)
Crusher	9.78
Finish mill 2/3	4.41
Raw mill 2/3	0.52
Cement packer	31.45

DISCUSSION

The study investigating SP-A serum as a marker of occupational lung disease in cement workers is rare in Indonesia. SP-A has been researched as a marker for various lung diseases, including examining serum levels of SP-A against interstitial lung disease, interstitial pneumonia, sarcoidosis of pulmonary fibrosis disease, ARDS, pulmonary TB, pneumonia, bronchiectasis, COPD, and silicosis.[7]

Another study reported increased SP-A and age associated with slower mucociliary clearance rates compared to young adults and decreased lung function. A decrease in the quality of humoral immunity, which is characterized by loss of high affinity blocking antibodies and an increase in self-reactive antibodies, has been reported in the elderly, resulting in decreased levels of IL-13 that trigger transcription of matrix metalloproteinases (MMP)-2, 9, 12, and 14, reducing MMP-1 synthesis, and synergistically with TGF-β increase fibroblast TIMP-1 which is a pro-fibrotic mechanism. [7]

In this study, based on respiratory complaints, the group with respiratory complaints had an average of 11.97 ng/ml, and the group without respiratory complaints had an average of 6.02 ng/ml. The difference in SP-A levels between the two groups was significantly different, with *P*=0.017. The results of this study are different from the study of Hideo Kobayashi et al in 2008 in patients with COPD who had respiratory complaints; serum SP-A levels increased significantly (*P*=0.01),[8] Study of Yoshio Kuroki's in 1998, with the results of SP-A levels were quite different between patients with respiratory complaints and controls (*P*<0.001).[9]

According to Akella study in 2013 in patients with COPD, asthma, bronchiectasis or other respiratory disorders, the surfactant function decreased due to alveolar macrophage activity, and released proteins, proteolytic enzymes, inflammatory mediators, reactive oxygen and nitrogen species, all of these chemical agents can reduce the availability of decreased functional capacity synthesis.[10]

Differences in SP-A levels based on smoking history in this study found SP-A levels in three groups, the smokers' group with an average of 6.07 ng/ml, the ex-smokers group with an average of 5.84 ng/ml, and the non-smokers' group with an average of 6.01 ng/ml. The results were not significantly different (*P*=0.819).

This study's results differ from the research conducted by Hideo et al in 2008 with the same variables: groups of active smokers, ex-smokers, and non-smokers. The results were significantly different between active smokers and ex-smokers (*P*<0.05), the results of the comparison between groups of active smokers and non-smokers (*P*=<0.01), and the comparison between a history of smoking and never smoking were not significantly different.[8] In the study of Fernandez-Real et al, which linked Sp-A levels with metabolite variables, the same results were obtained in the smoking and non-smoking groups.[11]

The difference in SP-A levels was based on the Brinkman Index in the three groups. However, there was no sample for severe IB, and the group with moderate IB had an average of 5.98 ng/ml, and the group with mild IB had an average of 5.91 ng/ml. The difference in SP-A levels between the two groups based on Brinkman Index showed that the results were not significantly different, with *P*=0.480

The study by Hideo et al in 2008 found that the relationship between serum levels of SP-A and the Brinkman Index in active smokers was significantly different (r=0.39; *P*<0.01).[8] In addition, Nomori et al concluded that there was a relationship but not related considerably between SP-A serum and the Brinkman index (r=0.53).[12]

Differences in SP-A levels based on the use of PPE, this study found SP-A levels in three groups, the group with poor PPE with an average of 6.40 ng/ml, the group with middle PPE with an average of 5.99 ng/ml, and the group with suitable PPE with an average of 6.32 ng/ml. The difference in SP-A levels between the three groups using PPE was not significantly different, with *P*=0.277. The Mengkidi study in 2006 reported no significant relationship between the use of PPE and impaired lung function in cement workers.[3] Another study said that the use of PPE depends on the high concentration of dust exposure; in this study, dust <5 microns in size is required and used when working in the factory area.[13]

The research subjects were grouped into workers >10 years with an average of 6.06 ng/ml and groups of workers <10 years with an average of 5.66 ng/ml. The difference in SP-A levels between the two groups obtained significantly different results with *P*=0.008. This study is in line with the research of Dutt et al in 2015, which found that workers who were directly or indirectly involved in mining activities were mainly exposed to silica dust after working for more than 20 years because the percentage of T cells that produced IL-13 showed a decrease. Along with increasing age, this causes a decrease in neutrophil function in chemotaxis.[14]

Differences in SP-A levels based on the work area with the results of SP-A serum levels in eight groups, the group in the cement packer working area with an average of 6.13 ng/ml, the group in the kiln working area with an average of 5.82 ng/ml, the group in the crusher working area with an average of 6.85 ng/ml, the group in the finish millwork area with an average of 5.72 ng/ml, the group in the quarry work area with an average of 5.71 ng/ml, the group in the raw mill working area with an average of 5.60 ng/ml, the group in silica crusher working area with an average of 6.37 ng/ml, the group in other areas with an average of 6.38 ng/ml.

The difference in SP-A levels between the eight groups based on the work area obtained results that were not significantly different from the value. The manufacture of cement uses a mixture of silica sand which contains free silica at varying levels, so that silicosis can occur in workers in the raw material area, cleaners, closed rooms, and slag milling.[15]

This study found SP-A levels in the research subject group or the exposed group, with an average of 6.02 ng/ml, and control subjects with an average of 4.50 ng/ml. The difference in SP-A levels between the exposed and control groups was different but not significant (*P*=0.084). In contrast, Spech et al identified a substantial relationship between silica exposure and the incidence of increased SP-A (*P*=0.001).[16]

Lesur et al performed a different study in 1993 with sheep exposed to silica as a subject with controls; there was a significant twofold increase in the silica-exposed group; based on this study, experimental animals can represent what happens to humans, but further research is still needed.[17] Another study showed an increase in SP-A in the blood serum in workers exposed to silica dust, starting from the occurrence of fibrosis, which resulted in alveolar damage and an increase in alveolar vasculature, which then resulted in vascular leakage that serum A was found in blood serum.[16]

In this study, the highest dust content was found in the cement packer area of 31.45 mg/m^3, followed by the crusher area of 9.78 mg/m^3, the finish mill area of 4.41 mg/m^3, and the raw mill area of 0.52 mg/m^3. Previous research in Indonesia found that the dust content in the cement packer area was 18.47

mg/m^3, the mining area was 20.23 mg/m^3, and the crusher was 14.98 mg/m^3, while the raw mill and finish mill areas were <10 mg/m^3. In the cement packer area, there is an increase in dust content. In the Tungu AM study, it was found that there was a decrease in total dust levels as well as a decrease in the prevalence of COPD and an increase in lung function among cement workers.[12]

According to Akella's research in 2013. Inhaled silica dust can inhibit surfactant secretion in AT-II cells, thereby increasing the intracellular phosphatidylcholine content. The threshold value (NAV) is the standard of environmental work factors recommended in the workplace so that workers can still deal with them without causing illness or health problems in their daily work for no more than 8 hours a day or 40 hours a day week. This NAV uses to replace the adverse effects of chemicals in the workplace. The unit of NAV of chemicals in the workplace air can be expressed in mg/m^3 of air. NAV for silica dust content based on the Circular Letter of the Minister of Manpower No. 01/MENNAKER/1997 is 0.05 mg/m^3 for silica cristobalite and tridymite, and 0.1 mg/m^3 for silica quartz and tripoli.[12,13,18]

LIMITATION

This study has several limitations. Sampling according to the inclusion criteria is difficult and the process of sending serum samples takes a long time so it is feared that it will interfere with the quality of the serum. The terrain used in sampling the dust content is difficult. Furthermore, some of the labels on the serum samples could not be identified. The lack of respondents and the limitations of related references are also limitations in this study.

CONCLUSION

SP-A levels in the research subject group or the exposed group compared with the control group were statistically different but insignificant. The relationship between serum SP-A levels with respiratory complaints, history of the respiratory tract, length of work, and age in the research subjects obtained statistically significant different results. The relationship between SP-A levels and the smoking history group and the IB group is different but statistically not significant. The relationship between SP-A levels and the PPE use group was statistically insignificant.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. Susanto AD. Pneumokoniosis. Journal of The Indonesian Medical Association. 2011;61(12):503–10.
2. Mwaiselage J, Bråtveit M, Moen B, Mashalla Y. Cement dust exposure and ventilatory function impairment: an exposure-response study. J Occup Environ Med. 2004;46(7):658–67.
3. Mengkidi D, Nurjazuli, Sulistiyani. Gangguan fungsi paru dan faktor-faktor yang mempengaruhinya pada karyawan PT. Semen Tonasa pangkep sulawasi selatan | Mengkidi. Jurnal Kesehatan Lingkungan Indonesia. 2006;5(2):59–63.
4. Stellman JM, International Labour Office. Encyclopaedia of occupational health and safety. 4th ed. Vol. 1. Geneva: International Labor Office; 1998. 10 p.
5. Salawati L. Silikosis. Jurnal Kedokteran Syiah Kuala. 2017;17(1):20–6.
6. Kolegium Pulmonologi dan Kedokteran Respirasi. Buku ajar pulmonologi dan kedokteran respirasi. 1st ed. Rasmin M, Yusuf A, Amin M, Taufik, Nawas MA, Rai IBN, et al., editors. Jakarta: UI Press; 2017.

7. Mazur W, Toljamo T, Ohlmeier S, Vuopala K, Nieminen P, Kobayashi H, et al. Elevation of surfactant protein A in plasma and sputum in cigarette smokers. Eur Respir J. 2011;38(2):277–84.
8. Kobayashi H, Kanoh S, Motoyoshi K. Serum surfactant protein-A, but not surfactant protein-D or KL-6, can predict preclinical lung damage induced by smoking. Biomarkers. 2008;13(4):385–92.
9. Kuroki Y, Takahashi H, Chiba H, Akino T. Surfactant proteins A and D: disease markers. Biochim Biophys Acta. 1998;1408(2–3):334–45.
10. National Institute for Occupational Safety and Health (NIOSH). Work-related lung disease surveillance report 2007 [Internet]. Division of Respiratory Disease Studies National Institute for Occupational Safety and Health. 2008. Available from: https://www.cdc.gov/niosh/docs/2008-143/pdfs/2008-143.pdf
11. Fernández-Real JM, Chico B, Shiratori M, Nara Y, Takahashi H, Ricart W. Circulating surfactant protein A (SP-A), a marker of lung injury, is associated with insulin resistance. Diabetes Care. 2008;31(5):958–63.
12. Nomori H, Horio H, Fuyuno G, Kobayashi R, Morinaga S, Suemasu K. Serum surfactant protein A levels in healthy individuals are increased in smokers. Lung. 1998;176(6):355–61.
13. Department of Labour South Africa. National Programme for the Elimination of Silicosis. 2007. p. 1–12.
14. Dutt KL. Sandstone quarry workers Karauli, Rajasthan, India. Retrieved from, Canberra: Australian National University. 2015;1–21. Available from: http://aravali.org.in/themes/upload/news/351161.pdf
15. Holmskov U, Thiel S, Jensenius JC. Collections and ficolins: humoral lectins of the innate immune defense. Annu Rev Immunol. 2003;21:547–78.
16. Spech RW, Wisniowski P, Kachel DL, Wright JR, Martin WJ 2nd. Surfactant protein A prevents silica-mediated toxicity to rat alveolar macrophages. Am J Physiol Lung Cell Mol Physiol. 2000;278(4):L713-8.
17. Lesur O, Veldhuizen RA, Whitsett JA, Hull WM, Possmayer F, Cantin A, et al. Surfactant-associated proteins (SP-A, SP-B) are increased proportionally to alveolar phospholipids in sheep silicosis. Lung. 1993;171(2):63–74.
18. Rinawati P. Coal worker's pneumoconiosis. Medical Journal of Lampung University. 2015;4(1):49–56.

Original Article

Lidocaine Nebulization Compared to Lidocaine Spray in Decreasing Pain, Cough and Breathless in Flexible Fiber Optic Bronchoscopy

Vita Ovaria, Yusup Subagio Sutanto, Ahmad Farih Raharjo

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret Surakarta – RSUD dr. Moewardi, Surakarta, Indonesia

Abstract

Background: Flexible optical fiber bronchoscopy (FFB) is a visual airway tract examination for diagnostic and therapeutic purposes. This procedure often causes discomfort for patients, such as cough, breathlessness and pain. Lidocaine is a topical anesthetic premedication used in bronchoscopy. This study compared the use of lidocaine nebulization and lidocaine spray in inhibiting pain, cough and breathlessness in complexity of flexible fiber optic bronchoscopy.
Methods: Pretest and posttest control group clinical study was conducted in patients prior to bronchoscopy at RSUD Dr. Moewardi from February to March 2020. The samples were taken by consecutive sampling technique, then randomly assigned into either lidocaine spray or nebulization. Cough and pain were assessed with VAS score while breathlessness was assessed with Borg score. The data were analyzed statically by using Chi-square test with $P<0.05$ was considered significant
Results: Cough scores were -17.78±11.66 for nebulization and -8.33±6.18 for spray ($P=0.005$). Pain score were -16.67±11.38 and -9.44±7.25 for nebulization and spray respectively ($P=0.045$). Borg score obtained the scores for nebulization and 0.06±0.42 for spray ($P=1.000$).
Conclusion: Both lidocaine nebulization and spray were effective in decreasing breathlessness during bronchoscopy. However, lidocaine nebulization was more effective in decreasing cough and pain.
Keywords: breathless, bronchoscopy, cough, lidocaine, pain

Corresponding Author:
Vita Ovaria | Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Sebelas Maret Surakarta / RSUD dr. Moewardi, Surakarta, Indonesia | vitaovaria@gmail.com

Submitted: May 28th, 2020
Accepted: August 3rd, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 319-27
https://doi.org/10.36497/jri.v42i4.368

INTRODUCTION

Flexible fiberoptic bronchoscopy (FFB) is a visual examination of the airways, also called airway endoscopy, that can visualize the tracheobronchial area. The FFB procedure is performed as a diagnostic tool to take airway and tissue mucus samples. Flexural fiberoptic bronchoscopy is the most commonly performed procedure for examining lung disease. Invasive measures for diagnosing and treating lung disease are quite developed along with advances in technology. Indications for this action are divided into diagnostic and therapeutic indications.[1,2]

Minimally invasive procedures in FFB often cause discomfort to the patient but can increase the value of diagnosis and result in more effective therapy. Minimizing contamination during invasive procedures is very important so that these actions do not cause secondary infections. This procedure is generally performed in patients using moderate sedation with intravenous premedication but may also be performed without sedation and general anesthesia. Patients with critical illnesses can also be treated with FFB to establish diagnosis and therapy. The patient considers the FFB procedure uncomfortable due to the side effects of the action taken. Discomfort and complications of this procedure include pain, coughing, and shortness of breath. The comfort and cooperation of the patient when it is carried out significantly affect the success of the action and affect the overall results to be achieved.[3–5]

Lidocaine is a topical anesthetic recommended as a premedication intervention in BSOL. Nebulized lidocaine as a premedication is expected to reduce pain, cough, and shortness of breath and eliminate unpleasant sensations during the procedure. The minimum effective dose should be used and should be used with caution in patients with advanced age, impaired liver function, or congestive heart failure. A well-established doctor-

patient relationship and *informed consent* are also expected to reduce discomfort in patients during FFB procedures. Research conducted by Sudarto et al. showed that administering anesthetic spray and nebulization comforts patients undergoing FFB procedures. Research by Dreher et al. showed that administration of lidocaine during nebulization was found to be well tolerated and safe compared to administration by injection. Bronchoscopy with general anesthesia is still an obstacle because it prolongs the duration of bronchoscopy, increases costs, and increases common complications, including hemodynamic disorders and respiratory depression.[4,5]

Research on the effect of nebulized lidocaine and spray on FFB premedication in reducing side effects of pain, cough, and shortness of breath has not been studied further. The results of this study are expected to show differences in the use of nebulized lidocaine and spray in reducing side effects in patients who will undergo FFB procedures at Doctor Moewardi Hospital Surakarta and can be applied to achieve better treatment results.

METHODS

This study was clinical research with the pretest-posttest control group design. The target population was patients who underwent BSOL procedures at Dr. Moewardi Hospital Surakarta in February-March 2020 until the sample was met. The method of selecting the research sample is determined by consecutive sampling. Each patient who met the study criteria on consecutive sampling was included in the study for a certain time until the required number of patients was met. Determination of the control group is the order of patients with odd numbers, and the treatment group is the order of patients with even numbers. There were 36 participants included and assigned into two groups, 18 participants for each group.

The inclusion criteria in this study were patients who would undergo bronchoscopy at Dr. Moewardi Hospital Surakarta in medical treatment, willing to take part in the study by signing informed consent, age ≥18 years, the patient was aware and was not diagnosed with mental disorder, able to see, read, write, and communicate verbally well, was cooperative and met the requirements for FFB procedure. The exclusion criteria in this study were patients who had allergies or intolerances to lidocaine, refused the study, could not see, read, write, and communicate well verbally, patients with heart disorders and severe risk measures, a severe lung disease with severe risk measures, poor general condition, hypoxia, coagulopathy or a hemorrhagic diathesis.

The patient presented to Dr. Moewardi Surakarta to take FFB action. Patients, as research subjects, were initially explained about the aims and objectives of study. All study subjects were explained about standard education on bronchoscopy. Research subjects willing to participate in the study were asked to sign an informed consent form. Subjects who met the inclusion criteria were given education. The research subjects were assigned into two groups by consecutive sampling, treatment and control groups. Participants who had been explained about standard education on bronchoscopy implementation and education were asked to fill out questionnaires. The first treatment group was given nebulized lidocaine 2% 5cc for premedication before the FFB procedure. The second treatment group was given 10% lidocaine spray 3 actuations in the oropharynx before the FFB procedure. The assessment of pain, cough, and shortness scores was carried out before and after the FFB action was completed, and then a statistical analysis of the results was carried out.

Data analysis was carried out using SPSS version 19 for Windows and data presentation using Microsoft Office 2010. All research data were tested for normality, and research data used the Shapiro-Wilk normality test since the sample was <50 subjects. This study used an unpaired sample so that the research data was tested with independent T-test if the data was normally distributed and Mann-Whitney test if the data was not normally distributed. In contrast, the paired group sample test used paired T-test if the data distribution was normal. Wilcoxon test is used for both normal and abnormal data

distribution.

RESULTS

This study was conducted on 36 participants who were equally assigned into two groups. Each group consisted of 18 participants, namely the nebulized lidocaine group and the lidocaine spray group. Research subjects who had been explained about standard education in implementing FFB were given an initial assessment. Initial assessment of pain using the VAS of pain, cough with the VAS of cough, and shortness of breath with the modified Borg scale. The initial assessment was carried out in the bronchoscopy room before the procedure.

The first group was given 10% 5cc nebulized lidocaine for premedication, while the second group was given 10% lidocaine spray three times actuation in the oropharynx for premedication before FFB. A second-stage assessment of pain, cough, and shortness was performed after the FFB was completed. The characteristics of the research subjects in this study were age, gender, occupation, education, Brigman's index, and comorbidities. The characteristics of the subjects of this study were categorical data presented in the form of frequency and percentage distributions.

Characteristics of research subjects were based on several components. The average age of patients undergoing bronchoscopy in the Nebulization group was 50.06±12.72 years, and the average age in the spray group was 60.61±12.45 years. Statistical test results obtained *P*=0.017, which indicated that there was a significant difference in patient characteristics based on age between patients in the nebulized and spray group.

Table 1. Characteristics of Research Subjects

Characteristics	Group		*P*
	Nebulization	Spray	
Age[a]	50.06±12.72	60.61±12.45	0.017
Gender[b]			
Male	14 (77.8%)	13 (72.2%)	1.000
Female	4 (22.2%)	5 (27.8%)	
Occupation[b]			
Laborer	2 (11.1%)	1 (5.6%)	
Housewife	2 (11.1%)	0 (0.0%)	
Pension	0 (0.0%)	1 (0.0%)	
Farmer	3 (16.7%)	9 (50.0%)	0.152
Civil Servant	2 (11.1%)	0 (0.0%)	
Self-employed	8 (44.4%)	7 (38.9%)	
Unemployed	1 (5.6%)	0 (0.0%)	
Education[c]			
Elementary School	4 (22.2%)	8 (44.4%)	
Junior High School	8 (44.4%)	3 (16.7%)	0.487
Senior High School	4 (22.2%)	6 (33.3%)	
College	2 (11.1%)	1 (5.6%)	
Index Brinkman[c]			
Non smoker	7 (38.9%)	7 (38.9%)	
Mild	4 (22.2%)	0 (0.0%)	0.852
Moderate	4 (22.2%)	11 (61.1%)	
Severe	3 (16.7%)	0 (0.0%)	
Contagious disease			
Plural effusion	3 (16.7%)	0 (0.0%)	
Hemoptysis	1 (5.6%)	0 (0.0%)	
Hydropneumothorax	1 (5.6%)	0 (0.0%)	
Hypertension	2 (11.1%)	0 (0.0%)	0.050
Pneumonia	5 (27.8%)	3 (16.7%)	
Chronic Obstructive Pulmonary Diseases	1 (5.6%)	1 (5.6%)	
Super Vein Cava Syndrome	1 (5.6%)	0 (0.0%)	
Others	4 (22.2%)	14 77.8%)	

Note=Numerical data is normally distributed, independent sample t test; [b] nominal categorical data; frequency (%), chi square/fisher exact test; declared significant if the test results in *P*<0.05.[c] Coordinal category: f (%) Mann Whitney test

Fourteen patients (77.8%) in the nebulization group were male and 13 participants (72.2%) in the spray group was male. Statistical test results obtained *P*=1.000 meaning there was no significant difference in patient characteristics based on gender in the nebulized and spray groups.

Based on the occupation of patients, 8 patients (44.4%) in the nebulization group were self-employed while in the spray group patients, 9 patients (50.0%) worked as farmers. The statistical test result obtained *P*=0.152, implying there was no significant difference in patient characteristics based on occupation between patients in the nebulized group and spray group.

Based on the education, eight patients (44.4%) in the nebulization group were junior high school graduate, while eight participants (44.4%) in the spray group were elementary school graduate. The statistical test results obtained *P*=0.487, meaning there was no significant difference in patient characteristics based on education between patients in the nebulized group and the spray group.

Based on IB, there were 7 patients (38.9%) in the nebulized group patients who did not smoke, while in the spray group, most of them were moderate smokers, amounting to 11 patients (61.1%). The statistical test results obtained *P*=0.852, implying there was no significant difference in patient characteristics based on IB between patients in the nebulized group and spray group.

Based on comorbidities, five patients (27.8%) in the nebulized group were diagnosed with pneumonia while majority of patients in the spray group had no comorbidities, 14 patients (77.8%). Statistical test obtained *P*=0.050, indicating that there was no significant difference in patient characteristics based on comorbidities between patients in the nebulized group and spray group. The characteristics of the research subjects can be seen in Table 1.

The difference and decrease in pre-post pain scores with nebulized lidocaine and spray are described in Table 2. Based on Table 2, the average pretest pain score in the nebulized group was 27.22±21.91, and the post-test pain score averaged 10.56±12.59. The difference in post-pre-nebulization pain score changes decreased by an average of 16.67±11.38. The pre-test pain score in the spray group had average score of 25.56±9.22, and the post-test pain scores an average of 16.11±7.78. The difference in changes in post-pre pain score in the spray group was revealed to have average decrease of -9.44±7.25.

Table 2. Test of Differences in Pain Scores Between the Nebulized Group and the Lidocaine Spray Group

Group	Painful			
	Pre	Post	*P*	Post – Pre
Nebulization	27.22±21.91	10.56±12.59	0.0001	-16.67±11.38
Spray	25.56±9.22	16.11±7.78	0.001	-9.44±7.25
P	0.135	0.043		0.045

Note=The results of the observations are described with mean SD, the unpaired group difference test did not pass the normality requirement (mann whitney); Buji different groups in pairs did not pass the requirements for normality (Wilcoxon rank test). Changes are declared significant if the test results in *P*< 0.05.

The nebulized group obtained *P*=0.0001, implying that the group experienced a significant change in pain scores. The spray group had value of *P*=0.001, which means that the spray group experienced a significant change in pain scores. The nebulization and spray treatments reduced the patient's pain scores. The subjects who were given the nebulization treatment experienced a decrease in pain scores more than the spray group and were statistically significant. This was evidenced in the unpaired difference test on the post-pre difference value (*P*=0.045). It can be concluded that lidocaine nebulization reduces pain scores more than spray.

Table 3. Differences in Cough Scores Between the Nebulized Group and the Lidocaine Spray Group

Group	Cough			
	Pre	Post	*P*	Post – Pre
Nebulization	25.00±15.43	7.22±8.26	<0,001	-17.78±11.66
Spray	25.56±11.49	17.22±8.95	0,001	-8.33±6.18
P	0.684	0.002		0.005

Note=The results of the observations are described by means of SD, the unpaired group difference test does not pass the normality requirement (mann whitney); The paired difference test did not pass the normality requirement (Wilcoxon rank test). Changes are declared significant if the test results in *P*<0.05.

The difference and decrease in pre-post cough scores with nebulized lidocaine and spray is outlined in Table 3. Based on Table 3, the pre-test cough scores in the nebulized group had an average score of 25.00±15.43 and the post-test cough scores

averaged 7.22±8.26. The difference in the post-pre nebulized cough score changes was decreased by an average of -17.78±11.66. Pre-test cough scores in the spray group had an average score of 25.56±11.49 and post-test cough scores averaged 17.22±8.95. The difference in post-pre cough score changes in the spray group was decreased by an average of -8.33±6.18.

The nebulized group had value of *P*<0.001, indicating that the group experienced a significant change in cough score. The spray group had value of *P*=0.001, suggesting that the spray group experienced a significant change in cough scores. The nebulization and spray treatments reduced the patient's cough scores, whereas the subjects who were given the nebulization experienced a greater reduction in cough scores than the spray group and were statistically significant. This was evidenced in the unpaired difference test on the post-pre difference value (*P*=0.005). It can be concluded that nebulization lowers cough scores more than spray.

Table 4. Test of Differences in Tightness Scores between the Nebulized Group and the Lidocaine Spray Group

Group	Congested			
	Pre	Post	*P*	Post – Pre
Nebulization	1.19±1.32	1.11±1.36	0.593	-0.08±0.55
Spray	1.94±0.73	1.89±0.58	0.564	-0.06±0.42
P	0.010	0.007		1.000

Note=The results of the observations are described by means of SD, the unpaired group difference test does not pass the normality requirement (mann whitney); b the paired difference test did not pass the normality requirement (Wilcoxon rank test). Changes are declared significant if the test results in *P*<0.05

The difference and decrease in pre-post shortness scores of nebulized lidocaine and spray are summarized in Table 4. Based on Table 4, the pretest score in nebulized group had an average of 1.19±1.32 and average post-test score of 1.11±1.36. The difference in the post-pre-nebulized dyspnea score in the nebulized group was reported to have an average decrease of -0.08±0.55. The score of pre-test tightness in the spray group had an average of 1.94±0.73 and an average post-test score of 1.89±0.58. The difference in score changes of post-pre breathlessness in the spray group had an average decrease of -0.06±0.42. The nebulized group had value of *P*=0.593 suggesting that the nebulized group experienced an insignificant change in the shortness score. The spray group had value of *P*=0.564, indicating means that the spray group also did not experience a significant change in the tightness score. Participants who had nebulization treatment experienced a decrease in shortness scores more than the spray group, although statistically insignificant (*P*=1.000).

DISCUSSION

This study aimed to determine the effectiveness of lidocaine using nebulization and spray techniques as a premedication for FFB by assessing shortness, cough, and pain scores. Lidocaine was proven to be effective in controlling cough and pain complaints by significantly decreasing VAS scores.

In contrast, lidocaine as a control of shortness of breath was shown to be less effective due to the decrease in the Borg scale score, which was not statistically significant. The basic characteristic and research variables were compared between the treatment group and control group by first testing the normality of data distribution as the basis for selecting statistical test to be used.

In this study, majority of the patients in the nebulization group were male, amounted to 14 patients (77.8%), and most of the patients in the spray group were male; 13 patients (72.2%). This is following research data reporting that men have a greater risk of lung cancer than women, so there were greater number of male patients who undergo bronchoscopy than women. Age is a risk factor for lung disease. Older age will affect the physiological condition, causing a decrease in the immune system. Diseases that can occur are shortness of breath and blood cough due to malignancy. The average age of patients who underwent bronchoscopy with nebulization was above 50 years and with spray was above 60 years.

Most participants in the nebulization group were self-employed, patients (44.4%), while the spray group patients mostly worked as farmers, with 9 patients (50.0%). Employment describes a person's socioeconomic history. Education can also affect the

incidence of lung diseases such as lung cancer. This relates to knowledge about using personal protective equipment at work and an unhealthy lifestyle.

In this study, majority of patients in nebulization group were junior high school graduates, 8 patients (44.4%). Most of the patients in the spray group were elementary school graduates, 8 patients (44.4%). The number and duration of smoking are the most significant risk factors for lung cancer. This can be seen through the Brinkman Index (IB). IB in the nebulization group participants who did not smoke, 7 patients (38.9%), while majority of the patients in the spray group were moderate smokers, 11 patients (61.1%).

Pain is a manifestation of unpleasant feelings which a person perceives, and its causes, in addition to nociceptive stimuli, are also psychological stimuli. Bronchoscopy may cause discomfort due to psychological stress and pain in patients' noses and throats (dysphagia). This perception is in the form of discomfort or unpleasant sensations and negative emotions interpreted as threats to the body. Lidocaine premedication plays a role in reducing the sensation of pain due to FFB.[6,7]

In this study, there was a decrease in pain through the VAS assessment. The use of nebulization and spray methods both reduce pain. However, the nebulization method was more effective in reducing pain than spray, following the results of this study which shows the difference in the average pain scores in the post-pre-nebulized group with spray, which has a significant value. It was revealed that post-pre-nebulization pain score had more significant decrease than the post-pre-spray pain score. Thus, it can be concluded that nebulization and spray can reduce the patient's pain score, but nebulization reduces pain scores more than lidocaine spray.[8,9]

The role of lidocaine in reducing pain through inhibition of transmission (one of a series of pain processes) of pain impulses through A-delta and unmyelinated C fibers from the periphery to the spinal cord. The action of lidocaine will block sodium channels which causes the electrical conduction process, which includes the inhibition of influx of Na-K ion pumps to prevent impulse conduction. Using a nebulizer, the administration of lidocaine is more effective since the nebulizer breaks down the active substance particles into tiny sizes of about 5 μm and enter the respiratory tract.[10–13]

The particle size of 5 μm has the potential to be deposited throughout the bronchial tree to the terminal bronchioles and alveoli by sedimentation. This deposition occurs due to the impaction of these particles in the upper respiratory tract due to air velocity and flows turbulence. Lidocaine diffuses through the membrane, which is a lipoprotein matrix consisting of 90% fat and 10% protein, into the axoplasm, then enters the sodium channel and interacts with receptors in it so that sodium channel blockade occurs and inhibits the depolarization process of nerve impulses so that pain stimuli can be inhibited.[10–13]

However, the study result does not support the research conducted by Sudarto et al., which reported no significant difference in pain reduction received by patients in the group using nebulization nor spray. This is possible because there were differences in number of samples and different characteristics in the research of Sudarto et al.[4,14]

Cough and hemodynamic turbulence at the time of bronchoscopy is an "emergence phenomenon" and is a daily clinical problem that is potentially dangerous because it may cause uncontrolled patient movement. Various techniques have been developed to help reduce cough, including administering intravenous opiates or administering intravenous or inhaled lidocaine as a premedication because systemic opiates and lidocaine have antitussive properties.[14,15]

In this study, there was a decrease in cough reflexes in patients assessed using the VAS scale for patients undergoing bronchoscopy with lidocaine premedication. Using nebulization and spray methods reduced the incidence of coughing, but the nebulization method was more effective than the spray. This follows the results of this study, where the difference in post-pre cough score changes in the nebulized group had a more significant decrease than in the spray group. Thus, both nebulization and spray

treatments reduced the patient's cough score, but the nebulization decreased the cough score more than the spray and was statistically significant.

The use of lidocaine was studied in Iran in 2011, reporting that the administration of 2% lidocaine 1.5 mg/kg BW intravenously reduced the incidence of coughing during extubation. Lidocaine works by inhibiting the transmission of RAR impulses and C fibers from the vagus nerve afferent pathways to the medulla oblongata as the cough center so that the cough reflex can be suppressed. Cough reflex block by lidocaine may occur because it depresses brainstem function by blocking peripheral receptors in the trachea and hypopharynx. Lidocaine will also block sodium (Na+) channels in sensory neurons so that action potential formation and neuronal conduction do not occur, triggered by various stimulation of airway afferent fibers, thereby reducing the occurrence of reaction potentials in the event of the cough reflex.

However, this study's results do not follow the research conducted by Keane et al., which concluded that nebulization or spray anesthesia had the same efficacy in suppressing cough during flexible fiberoptic bronchoscopy. This is because, in Keane et al.'s study, the nebulized and spray patient group were given 100 mg of lignocaine before being nebulized 2.5 ml of 4% lignocaine and 100 mg of lignocaine spray. Hence, the results obtained in cough scores were not significantly different.[4,16]

Symptoms of shortness of breath due to bronchoscopy are possible. This situation occurs due to increased psychic stress due to bronchoscopy action, which stimulates parasympathetic nerve activation, which will result in the release of acetylcholine from the post ganglion vagus nerve, which in turn causes acetylcholine to bind to muscarinic receptors (M3) in bronchial smooth muscle and results in increased respiratory rate and bronchospasm. This process is bridged by action potentials that occur across the cell membrane. Some neurotransmitters also act as neuro-modulators as well as agonists, where neurotransmitters will affect the sensitivity of receptors to other neurotransmitters such as glycine.[17,18]

In this study, there was a decrease in the manifestation of dyspnea in patients undergoing bronchoscopy with lidocaine premedication by using the Borg scale. Both nebulization and spray methods can reduce the incidence of shortness of breath. This is following the results of the study where the difference in the post-pre-nebulized shortness score in the nebulized group had a more significant average decrease than the spray group although it was not statistically significant, so it can be concluded that nebulization and spray methods did not have a significantly different effect in reducing the incidence of dyspnea in post bronchoscopy patients.

Several possibilities cause the results of this study to be insignificant; including the patients who were not hypoxic, had no previous complaints of shortness of breath and from the results of lung function measurements had good lung function values, so that the assessment of pre and post breathlessness scores of lidocaine administration was nebulization and spray did not have a significant impact.

This study also proved that there were no bronchoconstriction side effects, so participants were unlikely to be short of breath, and it is safe to use. A study by Michelle et al. compared the effects of nebulized anesthesia with spray. The study suggested no significant difference in the output between the administration of anesthesia as a premedication using the nebulization and spray methods.[19,20]

LIMITATION

This study has only proved the hypothesis that the effect of lidocaine premedication given by nebulization and spray can reduce pain and cough complaints in bronchoscopy patients. In contrast, the effect of other pre-medications has not been studied. Further research is still needed to prove the hypothesis of the effect of premedication other than lidocaine used to reduce complaints of pain, cough, and shortness of breath on bronchoscopy.

CONCLUSION

Lidocaine nebulization and lidocaine spray reduced pain in FFB patients where the lidocaine nebulization reduction score was higher than the lidocaine spray score. Nebulized lidocaine and lidocaine spray reduced cough in FFB patients, where the score of decreasing cough in nebulized lidocaine was higher than lidocaine spray. Nebulized lidocaine and lidocaine spray did not reduce shortness of breath in FFB patients (there was no difference).

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. Küpeli E, Feller-Kopman D, Mehta AC. Murray and nadel's textbook of respiratory medicine. In: Broaddus VC, Mason RJ, Ernst JD, King TE, Lazarus SC, Murray JF, et al., editors. Diagnostic bronchoscopy. 6th ed. Philadelphia: W.B. Saunders; 2016. p. 372–8.
2. Antony P, Deshmukh H. Bronchoscopic findings of flexible bronchoscopy: a one-year retrospective study in a tertiary care hospital. Int J Res Med Sci. 2018;6(2):591–6.
3. Martin-Loeches I, Artigas A, Gordo F, Añón JM, Rodriguez A, Blanch LL, et al. Current status of fiberoptic bronchoscopy in intensive care medicine. Medicina Intensiva (English Edition). 2012;36(9):644–9.
4. Sudarto, Soeroso NN, Hasibuan P, Eyanoer PC. Perbandingan kenyamanan pasien yang menjalani prosedur anestesi lokal secara spray dengan nebulisasi pada pemeriksaan bronkoskopi serat optik lentur. Jurnal Respirologi Indonesia. 2015;35(2):72–7.
5. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's review of medical physiology. 25th ed. McGraw-Hill Education/Medical; 2015. 642–646 p.
6. Karloh M, Palú M, Mayer AF. Methods for assessing functional capacity in patients with COPD. Con Scientiae Saúde. 2015;13(4):633–49.
7. Bailey PH. The dyspnea-anxiety-dyspnea cycle--COPD patients' stories of breathlessness: "It's scary /when you can't breathe." Qual Health Res. 2004;14(6):760–78.
8. Parmar D. Benefits of inspiratory muscle training in COPD patients. International Journal of Science and Research. 2015;4(9):680–4.
9. Crisafulli E, Clini EM. Measures of dyspnea in pulmonary rehabilitation. Multidiscip Respir Med. 2010;5(3):202–10.
10. Bose AA, Colt HG. Lidocaine in bronchoscopy: Practical use and allergic reactions. Journal of Bronchology. 2008;15(3):163–6.
11. Madan K, Biswal SK, Tiwari P, Mittal S, Hadda V, Mohan A, et al. Nebulized lignocaine for topical anaesthesia in no-sedation bronchoscopy (NEBULA): A randomized, double blind, placebo-controlled trial. Lung India. 2019;36(4):288–94.
12. Katzung BG, Masters SB, Trevor AJ. Farmakologi dasar dan klinik. 12th ed. Vol. 1. Jakarta: EGC; 2014. 512–514 p.
13. Syarif A, Estuningtyas A, Setiawati A, Muchtar A, Arif A, Bahry B, et al. Farmakologi dan terapi. 5th ed. Jakarta: Departemen Farmakologi dan Terapeutik fakultas Kedokteran Universitas Indonesia; 2017. 259–267 p.
14. Mittal S, Mohan A, Madan K. Ventricular tachycardia and cardiovascular collapse following flexible bronchoscopy: Lidocaine cardiotoxicity. J Bronchology Interv Pulmonol. 2018;25(2):e24–6.
15. Asano F, Aoe M, Ohsaki Y, Okada Y, Sasada S, Sato S, et al. Bronchoscopic practice in Japan: A survey by the Japan Society for Respiratory

Endoscopy in 2010. Respirology. 2013;18(2):284–90.

16. Keane D, McNicholas WT. Comparison of nebulized and sprayed topical anaesthesia for fibreoptic bronchoscopy. Eur Respir J. 1992;5(9):1123–5.
17. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: A useful metric for the cardiopulmonary patient. Intern Med J. 2009;39(8):495–501.
18. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British thoracic society guideline on pulmonary rehabilitation in adults: accredited by NICE. Thorax. 2013;68(Suppl 2):ii1–30.
19. Korttila K, Tarkkanen J, Tarkkanen L. Comparison of laryngotracheal and ultrasonic nebulizer administration of lidocaine in local anaesthesia for bronchoscopy. Acta Anaesthesiol Scand. 1981;25(2):161–5.
20. Handa A, Dhooria S, Sehgal IS, Agarwal R. Primary cavitary sarcoidosis: A case report, systematic review, and proposal of new diagnostic criteria. Lung India. 2018;35(1):41–6.

Original Article

Association Between D-Dimer Level with Clinical Severity and Radiological Imaging of Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang

Hafis Herdiman, Masrul Basyar, Oea Khairsyaf

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

Abstract

Background: D-dimer could be used as a biomarker to distinguish the severity of COVID-19. High D-Dimer levels are associated with increased clinical severity and poor radiological imaging. This study aims to identify the correlation between D-dimer levels with clinical severity and radiological features of confirmed COVID-19 patients at RSUP dr. M. Djamil Padang.

Methods: This was a cross sectional study of 202 COVID-19 confirmed patients at RSUP dr. M. Djamil Padang using medical record data from 1 January to 31 March 2021. The data were collected using convenience sampling technique and analyzed by Kruskal Wallis Test to determine the association between D-dimer levels with clinical severity and radiological features.

Results: Majority of patients were in age groups of below 50 and 50-59 years, with equal proportion between men and women, and were in moderate clinical severity (58,4%). Most radiological imaging was in severe degree of 91 patients (45%). The association between D-dimer levels and clinical degree of COVID-19 patients as well as the association between D-dimer levels and severity of radiological imaging of COVID-19 patients were statistically significant (*P*=0.0001).

Conclusion: Elevated D-dimer level was a common feature at COVID-19 confirmed patients. High levels of D-dimer were associated with increased clinical severity and severe radiological features in COVID-19 patients.

Keywords: clinical severity of COVID-19, D-dimer, radiological imaging of COVID-19

Corresponding Author:
Hafis Herdiman | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, RSUP Dr. M Djamil Padang, West Sumatera, Indonesia | parupadang@yahoo.com

Submitted: November 20th, 2021
Accepted: October 24th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 328–34
https://doi.org/10.36497/jri.v42i4.241

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 mainly due to the speed and scale of disease transmission.[1] On April 6, 2021 WHO recorded 131,309,792 confirmed cases of COVID-19, with a death rate of 2,854,276.[2]

Abnormal coagulation function is one of the factors thought to be associated with disease progression due to SARS-CoV-2 infection characterized by elevated levels of D-dimer based on laboratory blood tests. Xiaokang He et al conducted a study that pointed out a significant difference between D-dimer levels and the degree of disease. D-dimer levels were more likely to be high in patients with severe and critical cases than in patients with mild or moderate cases.[3]

This result was supported by a study conducted by Mert Ozen which stated that 63.3% of patients experienced an increase in D-dimer, and it tended to escalate as the patient's clinical condition worsened. Another study reported that clinically severe levels of D-dimer were significantly higher, and these levels increased significantly with disease severity. Based on these results, it is suspected that D-dimer levels can be a biomarker in determining disease severity and prognosis of COVID-19 patients due to the activation of diffuse inflammation and coagulopathy which are symptoms of severe disease.[4–6]

The severity of the disease could also be assessed from the radiological imaging of the patient. The main chest X-ray features observed in COVID-19 patients were bilateral, peripheral, predominantly lower lung opacity, described as hazy, ground glass opacity, and consolidation. A systematic review by Vidali et al obtained that most of the patients had consolidated chest radiographs (68%) and ground

glass opacity (48%) with bilateral pulmonary involvement and mostly distributed in the lower and peripheral lower lungs.[6]

Research conducted by Marco Francone et al. which used CT scores to assess the extent of lung involvement in patients with COVID-19 found that there was a statistically significant relationship between CT scores and D-dimer levels. The reliance on CT scans creates a huge burden on the radiology department and this makes chest X-rays (CXR) a substitute for CT scans, although CXR are considered less sensitive (the sensitivity of CXR is only 56%) for detecting pulmonary involvement in early-stage disease, but are useful for monitoring progression of early lung abnormalities in COVID-19, especially in critical patients who are treated in intensive care units because it is more practical and economical.[7,8]

METHODS

This was a cross-sectional study using secondary data that was conducted in COVID-19 isolation room of Dr. M. Djamil Hospital Padang from January to September 2021. The study population was all COVID-19 patients who were treated in the COVID-19 isolation room of Dr. M. Djamil Hospital Padang from January 1, 2021 to March 31, 2021.

Inclusion criteria were COVID-19 patients treated in the COVID-19 isolation room of Dr. M Djamil Padang from January 1 to March 31, 2021, had complete medical record data, age >18 years. Meanwhile, the exclusion criteria were pregnant patients with confirmed COVID-19 at the time of admission to isolation treatment and COVID-19 patients with comorbidities of malignancy and stroke at the time of admission to isolation treatment.

Radiological imaging was chest X-ray when the patient was first admitted (<48 hours), classified into severity score and validated by a radiologist. Scores were assessed based on pulmonary involvement. Score 0 if no pulmonary involvement, score 1 if pulmonary involvement ≤25%, score 2 with pulmonary involvement 25-50%, score 3 if pulmonary involvement 50-70%, and score 4 if pulmonary involvement ≥70%. The measurement results were declared mild if the total severity was 0-2, moderate if 3-5, and severe if 6-8.

Data analysis was carried out descriptively and analytically. Bivariate analysis was used to find the correlation between the independent and dependent variables using Kruskal Wallis test.

RESULTS

The basic characteristics of the study subjects are presented in Table 1. Majority of the age groups were less than 50 years and 50-59 years, each of which was 59 patients (29.2%). The proportion of patients by gender was the same as that of men and women (101 patients or 50%, respectively). Based on clinical symptoms upon admission to the hospital, moderate clinical symptom was the most common observed in 118 patients (58.4%). Majority of the patients (45.0%) had severe radiological features. The D-dimer levels ranged from 163 to >10000 ng/mL with a median of 1690.5.

Table 1. Basic Characteristics of Confirmed COVID-19 Patients treated at Dr. M. Djamil Hospital Padang (N=227)

Patient Characteristics	Total	%
Ages		
<50 years	59	29.2
50-59years	59	29.2
60-69years	52	25.7
≥70 years	32	15.8
Gender		
Male	101	50.0
Female	101	50.0
Clinical Severity		
Moderate	118	58.4
Severe	12	5.9
Critical	72	35.6
Radiological imaging (chest X-ray)		
Mild	78	38.6
Moderate	33	16.3
Severe	91	45.0
D-Dimer Level		
Median (min-max)	1690.5 (163 - >10000)	

The level of D-dimer in confirmed COVID-19 patients with moderate clinical grade was the lowest with a median of 865.5 ng/ml and ranged from 163 to >10000 ng/ml, while the highest was found in the critical grade of 3389 ng/ml. and ranged from 587 to >10000 ng/ml as shown in Table 2.

Table 2. Correlation of D-Dimer Levels with Clinical Severity of Confirmed COVID-19 Patients at Dr. M. Djamil Hospital Padang

Variable	Clinical Severity			*P*
	Moderate (n = 118)	Severe (n = 12)	Critical (n = 72)	
D-dimer level, ng/ml [median (min-max)]	865.5 (163 to >10000)	1964 (685 to >10000)	3389 (587 to >10000)	0.0001

Table 3. Correlation of D-dimer Levels with Radiological Imaging (Thorax X-ray) of Confirmed COVID-19 Patients at Dr. M. Djamil Hospital Padang

Variable	Radiological Imaging			*P*
	Mild (n = 78)	Moderate (n = 33)	Severe (n = 91)	
D-dimer level, ng/ml [median (min-max)]	621.5 (163 to >10000)	1458 (215 to >10000)	2987 (591 to >10000)	0.0001

Based on the results of the normality test of data distribution and the homogeneity of the data variance according to the clinical degree, the results were not normal and not homogeneous (*P* <0.05), so that the difference analysis was performed using Kruskal Wallis non-parametric test and obtained *P*=0.0001. It was stated that the D-dimer level was correlated to the clinical degree of confirmed COVID-19 patients treated at Dr. M. Djamil Hospital Padang in the period of 1 January to 31 March 2021. The level of D-dimer tended to increase along with the severity of the clinical degree.

Table 3 shows that D-dimer levels in confirmed COVID-19 patients with mild radiological features ranged from 163 to >10000 ng/ml with a median of 621.5 ng/ml. In patients with moderate radiological features, it ranged from 215 to >10000 ng/ml with a median of 1458 ng/ml, and in severe radiological features, it ranged from 591 to >10000 ng/ml with a median value of 2987 ng/ml.

Based on the results of the normality test of data distribution and the homogeneity of data variance according to the radiological feature, the results were also not normal and not homogeneous (*P* <0.05). Difference analysis was carried out with Kruskal Wallis non-parametric test and *P*=0.0001 was obtained. D-dimer levels were associated with the radiological features of confirmed COVID-19 patients treated at Dr. M. Djamil Hospital Padang on 1 January to 31 March 2021. The D-dimer level also tended to increase along with the degree of severity observed from the radiological imaging.

DISCUSSION

This study pointed out that the prevalence of COVID-19 was observed equally highest in both the age group of less than 50 years with a mean age of 37.70 years and the age group of 50-59 years with mean age of 54.91 years (29.2%, respectively). Study conducted in Jakarta by Surendra also received the similar results with the median age of 46 years and the highest range being at the age of 32-57 year.[9] This was also in line with the study from Viradanti et al which showed that the highest age range was 40-59 years (57.3%).[10] Surendra stated that younger age at the time of admission was generally associated with a greater distribution of younger age in the general population on Jakarta.[9]

Characteristics of patients by gender in this study were comparable between men and women. Yu et al obtained the same result of equal distribution between men and women (50%, respectively).[11] Study from Long et al had male as the majority of the subjects (57.4%).[12] Men are more susceptible to infection associated with increased reactivation of immunity to viral infections compared to women due to increased antibody production so that they are effectively resistant to infection.[13] Chen et al obtained more women as the study subjects because women in East Asia express higher ACE-2 receptors so they are more likely to be infected with SARS CoV-2.[14]

Most of the clinical severity were moderate (58.4%). The results obtained were due to confirmed cases of COVID-19 with moderate clinical severity had comorbidities so that further treatment was needed and could not be carried out in regional hospitals. Garcia-Alvarado et al in their study obtained similar results which stated that the most clinical severity was moderate (62.7%), followed by severe (21.5%), and critical (15.6%).[15] Long et al observed that the most clinical severity was severe (41.7%), followed by moderate (33.9%) and critical

clinical severity (24.3%).[12] A higher proportion of moderate symptoms in this study was also associated with exclusion criteria which excluded the comorbidities of stroke and malignancy, pregnancy, as well as younger age.

Chest X-ray (CXR) has a low sensitivity in diagnosing COVID-19 but has advantages over CT-scan which is more practical and easier to access.[16] The sensitivity of CXR is only 56%.[8] Based on the radiological imaging, almost half of the patients (45%) had severe degree, followed by mild degree (38.6) and moderate degree (16.3%). Study from Setiawati et al showed that severe degrees of CXR imaging were more visible in as many as 92 COVID-19 patients, followed by moderate degrees in as many as 90 patients and mild degrees in as many as 43 patients.[17]

On the other hand, study from Baratella in 140 patients stated that pulmonary involvement of 1–25% was found the most in as much as 41.4% patients, followed by the pulmonary involvement of 26–50% in 22.1% patients, pulmonary involvement of 51–75% in 18.6% patients, pulmonary involvement of 76–100% in around 12.9% patients and without pulmonary involvement in 5% patients.[18] Yasin observed that mild degree of CXR was the most common (65.7%), followed by moderate degree (23.4%) and severe degree (10.9%).[7]

D-dimer is an indirect marker of active coagulation and thrombin formation, which is released when plasmin, a fibrinolytic enzyme cleaves fibrin for reducing blood clotting and indicates an endovascular thrombotic process.[6] The levels of D-dimer in this study ranged from 163 to 10000 ng/mL with a median of 1690.5. Yu et al obtained that the median level of D-dimer was 700 (300-1600) ng/mL.[19]

Alterations in coagulation factors during SARS-CoV-2 infection, especially D-dimer, are associated with severe clinical symptoms and a positive relationship with the severity of lung damage (CURB-65).[6] Elevated D-dimer level indicates progressive severity of COVID-19 infection and is used as a predictor of the need for aggressive critical care.[20]

This study pointed out that D-dimer levels increased with clinical severity of the patients and a significant correlation was obtained (P<0.0001). Garcia-Alvarado et al in their study noticed that the median levels of D-dimer at moderate, severe, and critical levels were 208 (145-327) ng/mL, 262 (210-456) ng/mL, and 858.5 (386-932) ng/mL, respectively, with P=0.001.[15] Yao observed that the median D-dimer level increased about 7 times from moderate to critical clinical severity (4.76 [2.02-13.30] mg/L vs 0.6 [0.33-1.49] mg/L; P=0.000). Yao also reported that D-dimer level escalated significantly with the increasing clinical severity of COVID-19 (P=0.000).[21]

A meta-analysis conducted by Gungor et al in 34 studies stated that there was an association between high D-dimer levels and severe clinical conditions (weighted mean difference/ WMD=0.45 mg/L; 95% CI=0.34-0.56; P<0.0001). D-dimer levels were also analyzed as a binary variable using 12 studies and in 828 severe cases as well as 1757 non-severe cases; D-dimer levels that exceeded the upper limit (>500 ng/mL) were significantly associated with disease severity with an increased risk of 1.58 times. (RR=1.58; 95% CI=1.25-2.00; P<0.0001).[22]

The diagnostic sensitivity of D-dimer as a predictor of COVID-19 severity among 2014 patients in meta-analysis from Zhan et al ranged from 43–100% and specificity ranged from 57–89%. The sensitivity and specificity obtained in meta-analysis from Zhan et al were 77% (95% CI=58–89%) and 71% (95% CI=64–77%).[23] Elevated D-dimer level is a serious problem in COVID-19 and is associated with higher mortality. This is correlated with an 18-fold increased risk of death compared to patients with normal D-dimer levels.[24]

The pathogenesis of SARS-CoV-2 infection involves the binding of viral glycoproteins to ACE2 identified in the alveolar epithelium and endothelium along with continuous activation of the inflammatory response and coagulation pathways resulting in a pro-coagulation state. This predisposes to systemic microthrombotic changes leading to multiorgan failure and DIC.[6]

Based on this, D-dimer levels are related to the clinical severity of confirmed COVID-19 patients. It was found that D-dimer levels elevated significantly

with the increasing clinical severity of COVID-19. The relatively high level of D-dimer early in infection identified the administration of anticoagulants. Bleeding risk was assessed using the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score. It is not recommended to give anticoagulants if the IMPROVE score is >7, due to the risk of bleeding.[24]

This study also obtained that the higher the D-dimer level, the higher the severity of the radiological imaging (P<0.0001). The D-dimer levels in the study of Eroglu et al which differentiated CXR score of less than 5 and more than 5, were 500 (300-800) mg/L and 900 (0.6-1.3) mg/L, respectively with P<0.001.[16] Viradanti et al observed a significant relationship between D-dimer levels and radiological imaging scores assessed from CXR; the higher the D-dimer level, the higher the CXR score.[10]

A typical COVID-19 radiological feature in CXR is in the form of ground-glass opacity to predominance of consolidation along with disease progression. Although CXR is considered less sensitive for detecting early-stage lung involvement, they are useful in monitoring disease progression in COVID-19, especially in critically ill patients who are hospitalized intensively.[7] The existence of a relationship between D-dimer levels with CXR scores explained that coagulopathy associated with the severity of pulmonary parenchymal involvement in COVID-19 caused by dysregulation of coagulation due to excessive inflammatory mediators induced by SARS-CoV-2 infection.[10]

Recent studies have found micro- and macrothrombotic changes in the pulmonary microvasculature.[6] Clot formation in COVID-19 patients is rapid and difficult to degrade. Activation of the coagulation cascade is supported by endothelial tumefaction, pulmonary megakaryocytes in the capillaries and endothelium. This is due to the lung is the first target organ of SARS-CoV-2 infection, and the degradation of intra and extravascular fibrin in the alveolar and interstitial sacs results in diffuse alveolar damage.[25]

Binding of SARS-CoV-2 spike protein to the ACE2 receptor on respiratory epithelial cells will decrease the protective ACE2/Ang1-7/Mas axis, which will intensify PAI-1 expression.[25] The SARS-CoV-2 spike protein has a higher affinity for CD147 and extracellular matrix metalloproteinases which can induce the expression of various hematopoietic cells associated with thrombotic and inflammatory mechanisms in arteries and veins.[24]

Respiratory and pulmonary epithelium releases pro-inflammatory cytokines. The infiltrated immune cells are activated and attack normal lung tissue by releasing excessive cytokines. This cytokine will promote the expression of positive acute-phase proteins, TF, trypsin, and inhibit negative proteins (such as albumin). Trypsin activated matrix metalloproteinases will damage the basolateral membrane and the interstitial extracellular matrix. Endotheliopathy occurs in the infected capillaries to initiate a local hypercoagulable state. Quinine-bradykinin is activated by IL6 to stimulate the expression of tPA (tissue plasminogen activator) in endothelial cells. Fibrin deposition activates endothelial cells to express more IL8 which will suppress clot lysis time.[25]

Complementary C5b-9 in the vasculature of COVID-19 patients and neutrophil extracellular traps (NETs) may be associated with a prothrombotic mechanism.[73] NETs contribute to organ damage and promote thrombosis and fibrinolysis through lymphocyte/macrophage-like elastase.[25]

Based on this, there is a relationship between D-dimer levels with radiological features with coagulation dysregulation due to excessive inflammatory mediators induced by SARS-CoV-2 infection which then cause pulmonary parenchymal involvement in COVID-19. In Indonesia, the recommended prophylactic anticoagulant is Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) at a dose of 40 mg subcutaneous LMWH once daily, or 5000 units of subcutaneous UFH twice daily. Prophylactic anticoagulation is given while the patient is hospitalized, with monitoring for anticoagulant side effects such as bleeding or other complications. In critically ill patients, 40 mg of enoxaparin subcutaneously twice daily or 7500 units

of subcutaneous UFH three times daily is administered as a prophylactic anticoagulant.[24]

LIMITATION

This study had limitations with the samples and did not control for other factors in D-dimer levels which affected the clinical severity and radiological features of COVID-19 confirmed patients in Dr. M. Djamil Hospital Padang, so the potential for bias could occur in this study.

CONCLUSION

Characteristics of confirmed COVID-19 patients were comparable between men and women with the most age group of under 60 years, moderate clinical degree, and severe radiological feature. There was a correlation between D-dimer levels with clinical severity and radiological imaging of confirmed COVID-19 patients treated at Dr. M Djamil Hospital Padang.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed Pharmacother. 2020;129.
2. World Health Organization. Coronavirus (COVID-19) [Internet]. World Health Organization. 2021 [cited 2021 Jan 16]. Available from: https://covid19.who.int/
3. He X, Yao F, Chen J, Wang Y, Fang X, Lin X, et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Scientific Reports. 2021;11(1):1–7.
4. Ozen M, Yilmaz A, Cakmak V, Beyoglu R, Oskay A, Seyit M, et al. D-Dimer as a potential biomarker for disease severity in COVID-19. Am J Emerg Med. 2021;40:55–9.
5. Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808–17.
6. Vidali S, Morosetti D, Cossu E, Luisa M, Luisi E, Pancani S, et al. D-dimer as an indicator of prognosis in SARS-CoV-2 infection: a systematic review. ERJ Open Res. 2020;6(2):00260–2020.
7. Yasin R, Gouda W. Chest X-ray findings monitoring COVID-19 disease course and severity. Egyptian Journal of Radiology and Nuclear Medicine. 2020;51(1):1–18.
8. Pascarella G, Strumia A, Piliego C, Bruno F, del Buono R, Costa F, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. 2020;288(2):192–206.
9. 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.
10. Viradanti T, Kusmala YY. The relation between -dimer level and chest x-ray (CXR) scoring in COVID-19 patients: What we can learn from? In: Proceedings of the 12th Annual Scientific Meeting, Medical Faculty, Universitas Jenderal Achmad Yani, International Symposium on “Emergency Preparedness and Disaster Response during COVID 19 Pandemic” (ASMC 2021). 2021. p. 149–52.
11. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020;195:219–25.
12. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, et al. D-Dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. Biomed Res Int. 2020;2020:6159720.

13. Wen S, Prasad A, Freeland K, Podury S, Patel J, Subedi R, et al. Clinical characteristics and outcomes of COVID-19 in west virginia. Viruses. 2021;13(5):835.
14. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell. 2020;19(7):e13168.
15. García-Alvarado FJ, Muñoz-Hernández MA, Moran Guel E, González-Martínez MDR, MacÍas Corral MA, Delgado-Aguirre HA. Risk factors and clinical phenotypes associated with severity in patients with COVID-19 in northeast mexico. Vector Borne Zoonotic Dis. 2021;21(9):720–6.
16. Aydogan Eroglu S, Cagavi Z, Yildiz T, Karakurt Z, Interest Group O behalf of C. Can the usage of the chest x-ray scoring during hospitalization in patients with COVID-19 predict the severity of the disease? Turk Thorac J. 2021;22(3):190–8.
17. Setiawati R, Widyoningroem A, Handarini T, Hayati F, Basja AT, Surya ARD, et al. Modified chest x-ray scoring system in evaluating severity of COVID-19 patient in Dr. Soetomo General Hospital Surabaya, Indonesia. Int J Gen Med. 2021;14:2407–12.
18. Baratella E, Crivelli P, Marrocchio C, Bozzato AM, de Vito A, Madeddu G, et al. Severity of lung involvement on chest X-rays in SARS-coronavirus-2 infected patients as a possible tool to predict clinical progression: an observational retrospective analysis of the relationship between radiological, clinical, and laboratory data. J Bras Pneumol. 2020;46(5):1–8.
19. Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao X, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. J Thromb Thrombolysis. 2020;50(3):548–57.
20. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology. 2021;88(1):15–27.
21. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J Intensive Care. 2020;8(1):1–11.
22. Gungor B, Atici A, Baycan OF, Alici G, Ozturk F, Tugrul S, et al. Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: A systematic review and meta-analysis. Am J Emerg Med. 2021;39:173–9.
23. Zhan H, Chen H, Liu C, Cheng L, Yan S, Li H, et al. Diagnostic value of D-Dimer in COVID-19: A meta-analysis and meta-regression. Clin Appl Thromb Hemost. 2021;27:10760296211010976.
24. Mahardhika GS, Dharma Tedjamartono T, Buwono PW. High D-dimer and CRP levels in an asymptomatic COVID-19 patient: A case report and brief literature review. Seminar Nasional Riset Kedokteran. 2021;2:167–77.
25. Zhao R, Su Z, Komissarov AA, Liu SL, Yi G, Idell S, et al. Associations of D-Dimer on admission and clinical features of COVID-19 patients: A systematic review, meta-analysis, and meta-regression. Front Immunol. 2021;12:691249.

Original Article

Analysis of Clinical Manifestation at Admission and Comorbidity on Clinical Outcome of COVID-19 Patients In RSUDZA Banda Aceh

Heliyana Isma, Yunita Arliny, Dewi Behtri Yanifitri, Budiyanti, Teuku Zulfikar

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

Abstract

Background: Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus and has become a pandemic until now. Clinical outcomes in patients vary depending on many factors, such as demographics, vital signs, laboratory results, and comorbidities.

Methods: This study aims to analyze clinical outcomes in COVID-19 patients associated with the patient's general information (age, sex), demographic factors, admission vital signs, degree of symptoms at admission, blood laboratory results at admission, and comorbidities. This study is an analytic observational study with a cross-sectional design. All variables were examined based on medical records at the time of admission to the hospital. A multivariate analysis was conducted to determine what factors most influence clinical outcomes in treated COVID-19 patients.

Results: There were 183 COVID-19 patients included in this study with moderate to critical degrees. Factors that influence the clinical outcome of COVID-19 patients are the presence of comorbidities, old age, high blood pressure and heart rate, anemia, leukocytosis, and increased blood sugar and creatinine at admission. Multivariate analysis showed that clinical symptoms of severe COVID-19 were a factor that influenced poor clinical outcomes in COVID-19 patients, with OR=5.6 (95% CI=2.223-13.90).

Conclusion: Age, comorbidity, blood pressure, heart rate, hemoglobin, random blood glucose, and creatinine at admission influence the clinical outcome of admitted COVID-19 patients.

Keywords: Clinical outcome, comorbidity, COVID-19, degree of symptoms, demographic, laboratory result, vital signs

Corresponding Author:
Yunita Arliny | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, General Hospital Dr. Zainoel Abidin, Banda Aceh, Indonesia | nita.arliny@unsyiah.ac.id

Submitted: February 25th, 2022
Accepted: October 21st, 2022
Published: October 30th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 335–40
https://doi.org/10.36497/jri.v42i4.288

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11th 2020. This disease impacts high morbidity and mortality rates in at-risk populations. Based on the WHO report as of 27th October 2021, the incidence was 243,561,596 confirmed cases, with a recorded number of deaths of 4,947,777.[1]

The clinical manifestations of COVID-19 vary widely. At the time of admission, 20–51% of patients have at least one comorbidity, the most common being diabetes mellitus (10-20%), hypertension (10-15%), and other cardiovascular and cerebrovascular diseases (7-40%).[2] Patients with chronic obstructive pulmonary disease (COPD) have a 4-fold risk of clinically adverse events during COVID-19 infection.[3]

Epidemiological research shows that the severity of comorbidities affects the prognosis of COVID-19. Systematic data from 69 research results show the severity of COVID-19 and comorbidities worsen the prognosis of COVID-19.[3] The American Center for Disease Prevention and Control (CDC) states that the risk of symptom severity due to COVID-19 is increasing in the elderly group clinical manifestations in men tend to be more severe than women. Based on vital signs, a poor prognosis for COVID-19 occurs with high blood pressure and an increased respiratory rate. Several studies have shown that increased blood glucose levels and leukopenia will have a worse prognosis.[3]

Published epidemiology data showed that the severity of the disease was correlated to comorbidity and influenced the prognosis. Data from a systematic evaluation of 69 publications showed that the severity of COVID-19 and comorbidity affected the terminal prognosis of COVID-19. Based on data by the Centers for Disease Control and Prevention

(CDC), the severe degree of disease was enhanced in the group of older age and male rather than younger female. Based on the vital sign, a lower prognosis of COVID-19 were influenced by higher blood pressure and tachypnea. Based on the laboratory parameter, several studies showed that higher blood glucose and leucopenia were correlated to a worse prognosis.[3]

The increasing incidence and mortality rate of COVID-19 and no current study to prove those prognosis parameters, specifically in Rumah Sakit Umum Daerah Zainoel Abidin (RSUDZA), the center of several COVID-19 cases in Aceh, encourage us to research "Analysis of Demographic Factor, Vital Sign, Degree of Symptom, Laboratorium Result and Comorbidity to Clinical Outcome of COVID-19 Patients in RSUDZA Banda Aceh".

METHODS

This study is an analytic observational study with a cross-sectional design. The research was conducted from April to June 2021 by collecting all medical record data for COVID-19 patients admitted at the PINERE and RICU RSUDZA from April to June 2021 using a total sampling technique. Medical records used as research samples met the inclusion criteria, namely COVID-19 patients confirmed by RT PCR, aged ≥18 years with or without comorbidities (COPD, DM, CKD, Hypertension). Exclusion criteria were COVID-19 patients who returned home at their request or incomplete medical records.

Descriptive data will be presented as mean and standard deviation, whereas the nominal data will be given as percentages. Bivariate analyses were performed to compare several variables between the two outcome groups (good and bad outcomes) with Chi-square and Fisher-exact test. Clinical outcomes were considered good if the patient was discharged (declared cured and allowed to go home with negative repeat RT PCR results), while those were declared bad if the patient died while in treatment. Multiple logistic regression analysis was done to obtain odds ratio (OR) and a 95% confidence interval. Data analysis was performed using Statistical Program for Social Sciences (SPSS) for Windows, version 24.

The study protocol was approved by the Ethics Committee, Faculty of Medicine Syiah Kuala University, and dr. Zainoel Abidin Hospital Banda Aceh, June 21st, 2022, with ethical clearance number 127/EA/FK-RSUDZA/2021.

RESULTS

This study collected 183 data from the medical records of COVID-19 patients; no medical records were excluded. The severity of COVID-19 in this study consisted of 80 (43.72%) patients with moderate symptoms, 77 (42.08%) patients with severe symptoms, and 26 (14.21%) patients with acute symptoms. There were 80 (43,72%) patients at all degrees who did not have comorbidities patients with severe symptoms more accompanied by hypertension (66.67%) and DM (51.35%) compared to other symptoms, CKD, COPD and other comorbidities accompanied the rest.

Table 1. Relationship between demographic factors and clinical outcome of COVID-19

Variable	Clinical Outcome		Total (N=183)	*P*
	Good (N=126)	Bad (N=57)		
Sex				
Men	73 (65%)	39 (35%)	112 (100%)	0.178
Woman	53 (75%)	18 (25%)	71 (100%)	
Age (years)				
17–25	9 (82%)	2 (18%)	11 (100%)	0.0001
26–35	24 (96%)	1 (4%)	25 (100%)	
36–45	45 (87%)	7 (13%)	52 (100%)	
46–55	25 (64%)	14 (36%)	39 (100%)	
56–65	20 (51%)	19 (49%)	39 (100%)	
>65	3 (18%)	14 (82%)	17 (100%)	

Bivariate analysis using chi-square showed no significant relationship between sex and clinical outcome (*P*=0,178). However, age differences were significantly correlated to the clinical outcome (*P*<0,001). Samples with younger ages had a better clinical outcome rather than older ones. Patients with younger ages had a better clinical outcome than older ones (Table 1).

Relations of vital signs to clinical outcome saturation were displayed in Table 2 with a component of the parameter; only blood pressure

(*P*=0,020) and vital sign were blood pressure, heart rate, heart rate (*P*<0,001) who were correlated to respiratory rate, temperature, and oxygen clinical outcome.

Table 2. Vital signs and clinical outcomes in COVID-19

Vital Sign	Clinical Outcome		Total (N=183)	*P*
	Good (N=126)	Bad (N=57)		
Blood Pressure				
Normal	51 (80%)	13 (20%)	64 (100%)	0,020
Pre HT	48 (71%)	20 (29%)	68 (100%)	
HT 1	13 (57%)	10 (43%)	23 (100%)	
HT 2	14 (50%)	14 (50%)	28 (100%)	
Heart Rate				
Normal	101 (84%)	19 (16%)	120 (100%)	0,0001
Tachycardia	25 (40 %)	38 (60%)	63 (100%)	
Respiratory Rate				
Normal	2 (67%)	1 (33%)	3 (100%)	0,934
Tachypneu	124 (69%)	56 (31%)	180 (100%)	
Temperature				
Hypothermia	1 (50%)	1 (50%)	2 (100%)	
Normal	93 (68%)	44 (32%)	137 (100%)	0,705
Febrile	32 (73%)	12 (27%)	44 (100%)	
Oxygen Saturation				
Normal	2 (100 %)	0 (0%)	2 (100%)	0,339
Desaturated	124 (69%)	57 (31%)	181 (100%)	

There is a statistically significant relationship between the degree of symptoms of COVID-19 and the clinical outcome of COVID-19 patients (*P*<0.001). Subjects with moderate symptoms tend to have an excellent clinical outcome, while patients with acute symptoms tend to have poor clinical outcomes (Table 3).

Table 3. Relationship between vital Relationship between degree of disease and the clinical outcome of COVID-19

Degree of Disease	Clinical Outcome		Total (N=183)	*P*
	Good (N=126)	Bad (N=57)		
Moderate	75 (94%)	5 (6%)	80 (100%)	0,0001
Severe	48 (62%)	29 (38%)	77 (100%)	
Critical	3 (12%)	23 (88%)	26 (100%)	

The results of blood laboratory tests showed that hemoglobin (*P*=0.025), leukocytes (*P*=0.001), random blood glucose (*P*=0.0001), and serum creatinine (*P*=0.0001) were significantly related to clinical outcomes in COVID-19 patients (Table 4).

Analysis of comorbidity and clinical outcome of COVID-19 were displayed in Table 5**,** indicating the significant relations between comorbidity and clinical outcome of COVID-19 (*P*<0,001). Samples without comorbidity were likely to have better outcomes than comorbidity ones.

Table 4. Relationship between blood laboratory results and the clinical outcome of COVID-19

Laboratorium result	Clinical Outcome		Total (N=183)	*P*
	Good (N=126)	Bad (N=57)		
Hemoglobin				
Normal	113 (72%)	44 (28%)	157 (100%)	0,025[1]
Anemia	13 (50%)	13 (50%)	26 (100%)	
Leukocyte				
Normal	81 (79%)	21 (21%)	102 (100%)	0,001[1]
Leukocytosis	45 (56%)	36 (44%)	81 (100%)	
Thrombocyte				
Thrombocytopenia	30 (67%)	15 (33%)	45 (100%)	
Normal	92 (71%)	38 (29%)	130 (100%)	0,439[1]
Thrombocytosis	4 (50%)	4 (50%)	8 (100%)	
Random Blood Glucose				
Normal	107 (75%)	35 (25%)	142 (100%)	0,0001[1]
High	19 (46%)	22 (54%)	41 (100%)	
Ureum				
Low	5 (83%)	1 (17%)	6 (100%)	
Normal	49 (71%)	20 (29%)	69 (100%)	0,725[2]
High	72 (67%)	36 (33%)	108 (100%)	
Creatinine				
Low	90 (84%)	17 (16%)	107 (100%)	
Normal	27 (64%)	15 (36%)	42 (100%)	0,0001[1]
High	9 (26%)	25 (73%)	34 (100%)	

Note=[1]Chi-Square test; [2]Fisher's exact test

Table 5. Relationship between comorbidity and the clinical outcome of COVID-19

Comorbidities	Clinical Outcome		Total (N=183)	*P*
	Good (N=126)	Bad (N=57)		
No comorbidity	76 (95%)	4 (5%)	80 (100%)	0,0001
Hypertension	22 (56%)	17 (44%)	39 (100%)	
Diabetes Mellitus	19 (51%)	18 (49%)	37 (100%)	
CKD	1 (8%)	12 (92%)	13 (100%)	
COPD	1 (33%)	2 (66%)	3 (100%)	
Others	7 (64%)	4 (36%)	11 (100%)	

Multivariate analysis of all variables (Table 6) was tested by logistic regression. It showed that age, the severity of the disease, comorbidity, and heart rate were correlated to the clinical outcome of COVID-19 patients with the *P*<0,05 and severity of disease with the *P*=0.0001 (OR=5.568; 95% CI=2.229–13.908). It means that severe disease would worsen clinical outcomes 5.6 times higher rather than another variable.

Table 6. Multivariate analysis of factors that affected the clinical outcome of COVID-19

Variable	*P*	OR	95% CI	
			Lower	Upper
Age	0,001	20,429	3,548	117,623
COVID-19 symptom	0,0001	5,568	2,229	13,908
Comorbidities	0,002	1,681	1,212	2,332
Blood Pressure	0,486	1,175	0,746	1,852
Heart Rate	0,032	2,86	1,092	7,492
Leucocyte	0,657	1,244	0,474	3,267
Random Blood glucose	0,102	2,283	0,85	6,134
Constanta	0,000	0,000	-	-

DISCUSSION

Based on gender, there are more people with COVID-19 males, with a proportion of 61.2%. This is supported by Karyono et al, which shows that more male suffers from COVID-19 than females.[4] This is thought to be due to the higher expression of angiotensin-converting enzyme-2 (ACE2), which male sex hormones may regulate.[5] The results of this study showed that there was no significant difference between gender and clinical outcome (p=0.178); this is following Zhang et al, which stated that there was no difference in the ratio of male to female sex in the outcome and severity of COVID-19 symptoms.[6]

There was a significant age difference in this study, with the highest incidence at the age of 36–45 years, but worse clinical outcomes were higher in the elderly in the age group of 56–45 years. This is under research by Karyono et al, which stated that almost a third of COVID-19 infections were in the young age group, but the highest mortality rate occurred in the elderly.[4] Older patients, especially those aged 65 and over with comorbidities, have an increased rate of intensive care unit (ICU) admission and death from COVID-19.[3]

In the vital signs variable, blood pressure (*P*=0.020) and heart rate (*P*=0.0001) showed significant differences in this study. The results of this study follow Karyono et al and Zhang et al which showed that cardiovascular disorders and high blood pressure were a greater risk for mortality.[4,6] Respiratory rate did not have a significant relationship (*P*=0.394) between the two groups, but 98.4% of subjects had an increased respiratory rate. This is different from Chatterjee et al, who stated that when oxygen saturation monitoring is not available, a respiratory rate of more than 22 times per minute is a marker of worsening COVID-19.[7]

In this study, the patient's temperature at admission had no significant relationship with clinical outcomes. This is under a study by Tharakan et al, which stated that higher body temperature at the initial clinical symptoms did not show a significant relationship with mortality, even though an increase in temperature was a predictor of the severity of viral infections in general.[8]

In this study, the oxygen saturation variable showed no significant relationship with clinical outcome (*P*=0.339), in contrast to the study by Mejia et al, which stated that oxygen saturation below 90% on admission was a predictor of death in hospitals in COVID-19 patients. Acute hypoxemia enhances various cytotoxic functions of neutrophils and triggers hyperinflammation. This is closely related to the occurrence of progressive lung tissue damage after the formation of the initial injury.[9]

This study found a statistically significant relationship between the degree of symptoms and the clinical outcome of COVID-19 patients (*P*=0.0001). It is the most dominant in multivariate analysis with OR=5.568 (95% CI=2.229–13.908). Based on a meta-analysis by Chidambaram et al, it

is shown that the severity of symptoms is closely related to COVID-19 mortality. The risk of death is higher in patients with increasing age, male, dyspnea, diabetes, hypertension, congestive heart failure, and the disease's severity.[10]

This study found that leukocyte levels were associated with clinical outcomes in COVID-19 patients (*P*=0.001). Study of Zhang et al showed that the leukocyte count was higher in patients with severe symptoms and became a more prominent marker of inflammation, a high risk of mortality, and a marker of secondary bacterial infection.[6]

Examination of blood glucose while also significantly related in this study. This was supported by Wang et al that blood glucose levels were a significant risk factor for death. Low serum hemoglobin and creatinine levels are also associated with the clinical outcome of COVID-19. Patients with high blood glucose levels are 58% more likely to develop more severe symptoms and 3.22 times more likely to die from COVID-19.[11]

In this study, comorbidities were associated with the clinical outcomes of COVID-19 patients. The most common comorbid disease was hypertension (21.3%), followed by diabetes mellitus (20.2%). The study by Karyono et al stated that COVID-19 patients had higher rates of hypertension, diabetes, and cardiovascular disease. Patients with comorbidities should avoid infection with SARS-CoV-2 because they are prone to poor prognoses.[4] Hyperglycemia and diabetes mellitus trigger the acceleration of viral replication by forming reactive oxygen species (ROS) in cellular mitochondria, mainly monocytes, which will activate factor 1α, which triggers hypoxia.[12]

Most of the population of Banda Aceh City has risk factors for diabetes and obesity due to the habit of high fat and high sugar intake and lack of physical activity. Data from the Banda Aceh City Health Office in 2018 showed 619 people with general obesity and 839 people with central obesity.[13] Another comorbid is CKD which is related to immune function dysregulation, which increases the risk of death in COVID-19 patients. ACE2 receptors are overexpressed in tubular cells, increasing serum creatinine as a marker of impaired kidney function.[5]

Cardiovascular disease is exacerbated by de novo COVID-19 infection. The SARS-CoV-2 agent that causes COVID-19 will migrate to the heart muscle through alveolar-capillary diffusion transport, which will eventually cause myocarditis. Conditions exacerbated by hypertension and coronary heart disease will increase the incidence of heart injury. Irregular regulation of the heart and blood vessels due to inflammation causes heart failure. The condition of old atherosclerotic formations can also cause the fragments to rupture, thus blocking the coronary arteries and eventually triggering a heart attack due to myocardial infarction.[14]

LIMITATION

-

CONCLUSION

There is a relationship between age and the clinical outcome of COVID-19 patients, young people are more susceptible to infection, but old age has a higher mortality. Increased blood pressure and heart rate are related to clinical deterioration in COVID-19 patients. Subjects with moderate symptoms tend to have good clinical outcomes, while those with acute symptoms tend to have poor clinical outcomes. The degree of symptoms of COVID-19 is the most dominant and statistically influential factor. Leukocyte and blood sugar levels during and with comorbidities significantly correlate with the clinical outcomes of COVID-19 patients. The most common comorbidities are hypertension, diabetes mellitus, and CKD, so they must be treated more intensively to prevent mortality.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. World Health Organization. Weekly epidemiological update on COVID-19 - 2 November 2021 [Internet]. World Health Organization. 2021 [cited 2021 Oct 27]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---2-november-2021
2. Guan W jie, Liang W hua, Zhao Y, Liang H rui, Chen Z sheng, Li Y min, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. European Respiratory Journal. 2020;55(5):640.
3. 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.
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. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of sex, age, and comorbidities with mortality in COVID-19 patients: A systematic review and meta-analysis. Intervirology. 2020;64(1):36–47.
6. Zhang J jin, Dong X, Cao Y yuan, Yuan Y dong, Yang Y bin, Yan Y qin, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730–41.
7. Chatterjee NA, Jensen PN, Harris AW, Nguyen DD, Huang HD, Cheng RK, et al. Admission respiratory status predicts mortality in COVID-19. Influenza Other Respir Viruses. 2021;15(5):569–72.
8. Tharakan S, Nomoto K, Miyashita S, Ishikawa K. Body temperature correlates with mortality in COVID-19 patients. Crit Care. 2020;24(1).
9. Mejía F, Medina C, Cornejo E, Morello E, Vásquez S, Alave J, et al. Oxygen saturation as a predictor of mortality in hospitalized adult patients with COVID-19 in a public hospital in Lima, Peru. PLoS One. 2020;15(12):e0244171.
10. Chidambaram V, Tun NL, Haque WZ, Gilbert Majella M, Kumar Sivakumar R, Kumar A, et al. Factors associated with disease severity and mortality among patients with COVID-19: A systematic review and meta-analysis. PLoS One. 2020;15(11):e0241541.
11. Wang W, Shen M, Tao Y, Fairley CK, Zhong Q, Li Z, et al. Elevated glucose level leads to rapid COVID-19 progression and high fatality. BMC Pulm Med. 2021;21(1):64.
12. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nature Reviews Endocrinology. 2020;17(1):11–30.
13. Ismardiani Y. Hubungan kualitas hidup pada penderita diabetes mellitus tipe II di wilayah kerja Puskesmas Jaya Baru Kota Banda Aceh tahun 2019. [Banda Aceh]: Universitas Muhammadiyah Aceh; 2019.
14. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543–58.

Literature Review

Therapeutic Bronchoscopy in Benign Central Airway Obstruction

Mia Elhidsi, Budi Prasetio Nugroho, Wahju Aniwidyaningsih

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia

Abstract

Benign central airway obstruction (BCAO) may occur in patients with post-intubation, tracheostomy, tuberculosis and non-tuberculosis infections, tracheal wall abnormalities, endobronchial benign tumors, vascular abnormalities, benign thyroid tumors and external mechanical compression. The management of BCAO is based on the underlying disease and requires multidisciplinary joint decisions from interventional pulmonology, thoracic surgery, radiology and anesthesia. Therapeutic bronchoscopy for the management of BCAO emergencies includes balloon dilation, stents and lasers.

Keywords: Therapeutic bronchoscopy, BCA (BCAO), balloon dilation, stents, laser

Corresponding Author:
Mia Elhidsi | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia

Submitted: September 25th, 2020
Accepted: June 21st, 2022
Published: October 30th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 341–6
https://doi.org/10.36497/jri.v40i3.361

INTRODUCTION

Benign central airway obstruction (BCAO) may occur in patients after intubation, tracheostomy, tuberculosis infection, surgery, sarcoidosis, polychondritis, and benign endobronchial tumors tracheobronchomalacia (TBM), external mechanical compression, transplantation and idiopathic.[1–3] BCAO requires multidisciplinary collaboration, including radiologists, thoracic surgery, interventional pulmonologists, and anesthesiologists.[2]

Bronchoscopy and its devices can serve as therapeutic tools, external radiation, and chemotherapy.[1] Examination of major airway disorders, including oropharynx, larynx, vocal cords, and tracheobronchitis system, and their management can use a rigid bronchoscope with a flexible bronchoscope.[2,4] This narrative review explores the variants of BCAO and therapeutic bronchoscopy in management of BCAO.

DEFINITION AND CLASSIFICATION OF CENTRAL AIR TRACT OBSTRUCTION

Central airway obstruction is occlusion of >50% of the trachea, main bronchi, intermedius bronchi, and lobar bronchi.[3] Histological anatomy of the trachea consists of 4 layers, namely the deep mucosal layer, submucosal layer, muscle and cartilage, and adventitia layer, including lymph nodes and connective tissue (Figure 1).

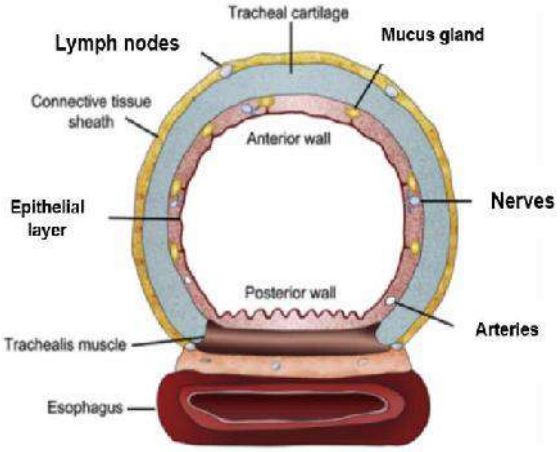

Figure 1. Trachea anatomy, horseshoe-shaped cartilaginous ring on the anterior-lateral tracheal wall.[3]

The anterior trachea is composed of 16–22 C-shaped cartilaginous rings. The function of tracheal ring is to maintain airway patency during expiration so that it does not collapse. The posterior tracheal wall is devoid of cartilage, only composed of smooth muscles and tracheal muscles. The length of trachea is about 10-12 cm in adults, measured from the cricoid to the carina (craniocaudal). The coronal diameter of trachea in male is about 13–25 mm and in women is about 10–21 mm; the thickness of tracheal wall is about 1–3 mm.[2]

Table 1. Classification of tracheal obstruction based on the severity of narrowing of the tracheal cross-sectional area.[3]

Level of obstruction	Description of narrowing of the tracheal cross-sectional area
1	Normal: no narrowing of the tracheal cross-sectional area
2	Mild: narrowing of the tracheal cross-sectional area <50%
3	Moderate: narrowing of the tracheal cross-sectional area 51 – 70%
4	Severe: narrowing of the tracheal cross-sectional area > 71%

The mild narrowing reduces the cross-sectional area of trachea by 50%, and the pressure drop is the same as the glottis closure so that it does not cause symptoms. Moderate obstruction reduces the cross-sectional area of trachea by 51–70%, causing various symptoms. There is a significant decrease in pressure at high airflow, for example, during exercise. However, patients who perform mild activities are usually asymptomatic with moderate obstruction. Severe obstruction, i.e., reduction of tracheal cross-sectional area >71%, causing a significant decrease in pressure even with low airflow, causing symptoms at rest and mild activity, requiring immediate treatment, classification of obstruction based on the severity of narrowing of the tracheal cross-sectional area is outlined in Table 1.[3]

Signs and symptoms of BCAO conform the etiology, location, and severity of the underlying disease. Signs and symptoms which often perceived by patients include shortness of breath during activity, shortness of breath, stridor, and chronic wheezing. Clinicians often make a differential diagnosis of asthma and chronic obstructive pulmonary disease (COPD). Stridor often occurs when the diameter of the tracheal stenosis is <5 mm, occurs during rapid and deep inspiration by opening the mouth.[5]

BCAO MECHANISM

Benign central airway obstruction is obstruction of the central airways that, including the trachea and main bronchi, is caused by other than malignancy. The mechanism of airway obstruction is due to intraluminal lesions, extrinsic compression, and weakness of the tracheal cartilage leading to dynamic tracheobronchial collapse. The diagnosis of benign central airway obstruction is often delayed because of atypical symptoms. Several diseases may lead to BCAO, as summarized in Table 2.[5,6]

Table 2. Diseases that cause BCAO[5–7]

Abnormalities/lesions	Underlying disease
Post-traumatic	Post-tracheal intubation injuries
	Post tracheostomy injury
	Tracheobronchial stenosis associated with stent placement
	Granulation tissue due to foreign body aspiration
	Respiratory tract trauma
	Radiation
	Toxic gas inhalation
Inflammatory disease of the respiratory tract	Granulomatosis polyangiitis
	Amyloidosis
	Sarcoidosis
	Idiopathic laryngotracheal stenosis
Endobronchial benign tumour	Squamous cell papilloma
	Papillomatosis
	Hamartoma
	Leiomyoma

Abnormalities/lesions	Underlying disease
Endobronchial benign tumour	*Lipoma*
	Fibroma
	Neurogenic tumours
	Pleomorphic adenoma
	Mucus gland adenoma
	Oncocytoma
	Tracheobronchopathia osteochondroplastica
Extrinsic compression	Lymphadenopathy
	Broncholithiasis
	Fibrosing mediastinitis
	Thyroid disease
	Goiter
	Cysts
	Thyroiditis
	Vascular disease
	Right aortic arch
	Double aortic arch
	Pulmonary artery sling
	Left carotid artery anomaly
	Aortic Aneurysm
	Mediastinal Cyst
	Abnormalities of the chest wall and spine
	Kyphoscoliosis
	Pectus excavatum
	Straight back syndrome
Infectious disease	Virus
	Bacteria
	Mycobacterium
	Mold
	Parasite
Dynamic expiratory narrowing	Tracheobronchomalacia
	Excessive dynamic airway collapse
Post-surgery	Anastomotic surgery
	Post pneumonectomy syndrome

THERAPEUTIC BRONCHOSCOPY

Therapeutic bronchoscopy is performed for central airway stabilization in airway obstruction and assessment for resection. Obstruction cases that are unresectable by therapeutic bronchoscopy are an option for palliative or definitive therapy to improve the quality of life and prolong the patient's life. Airway prosthetics that can be applied in bronchoscopy include silicone/ metallic stents, dilators, and laser invasive procedures. (Algorithm for the management of benign and malignant BCAO in Figure 2).[8–10]

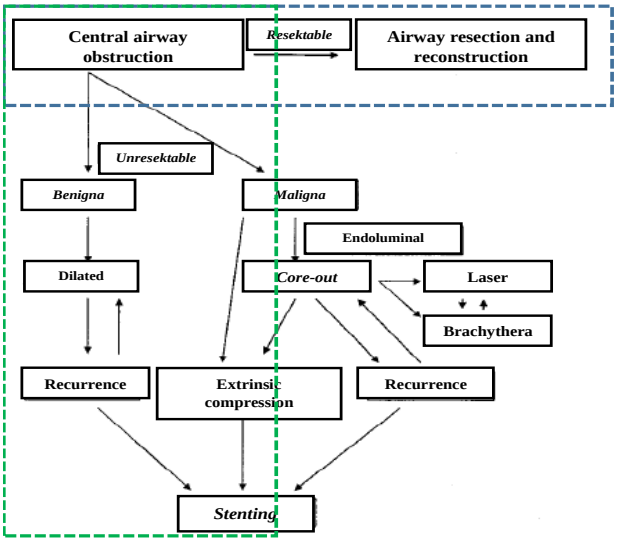

Figure 2. Algorithm for the management of CAO with therapeutic bronchoscopy. The box with dotted lines shows the management flow of BCAO.[10]

Stent

Installation of a stent with a rigid bronchoscope is usually performed under general anesthesia with or without muscle relaxants. While using a flexible bronchoscope, the patient may be subjected to local anesthesia and sedation. General anesthesia using induction of fentanyl 2.5ug/kg BW and propofol 2.0mg/Kg BW followed by maintenance with propofol 7–8mg/kg BW/hour reduced to 5–6mg/kg BW/hour after 15 minutes.[6,9,10]

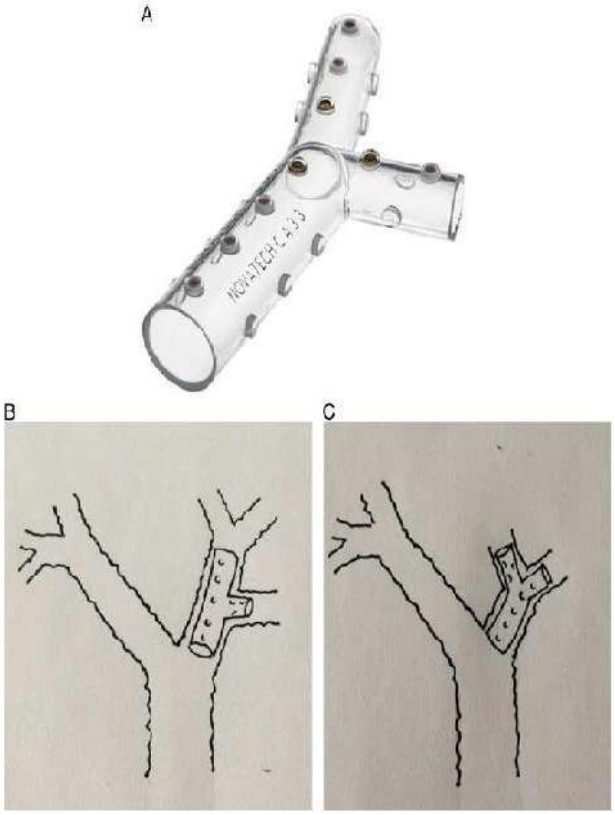

Figure 3. Ochy stent inserted into the right main bronchus: (A) Oki stent (Novatech), (B) Oki stent branching in the Upper-division, (C) Oki stent inserted into the right main bronchus, post-lobectomy. The right main bronchus appears to be shorter.[14]

There are 2 types of stents, namely silicone and metallic. Each type of stent is used depending on the case of stenosis and its cause. In cases of malignancy, metallic stents are often chosen to prevent tumor growth into the intraluminal, which are difficult to remove and have low migration incidence. Metallic stents are covered (silicone or polyurethane sheath) and uncovered. Examples of metallic stents are ultra-flex, wall stent and Silmet for straight shapes; Metallic Y-stents such as Ecostent. For the case of BCAO, the use of metallic stents should be avoided due to higher complications and difficult to remove. Silicone stents are recommended for OSNSJ since they are easy to remove, reposition, and cost less than metallic stents. Types of silicone stents such as Dumon and Spigots stents are easily detected by radiology because the base material is radio-opaque (Figure 3).[6,10–13]

Stent placement is performed by first determining the stent diameter and length covering the healthy areas proximal and distal to the stenosis, each about 5–10 mm. The type of stent used must be adjusted to the anatomic location, type of stenosis, underlying disease and risk of complications. Bronchoscopy experience helps in establishing the required stent diameter and length. Rigid diameter bronchoscopes may help in determining the diameter of stent. Generally, stents with a 14–16 mm diameter are used for tracheal stenosis and 10–12 mm for stenosis in the main bronchus.[3,6,10,13]

Amount 24 hours post stent placement, bronchoscopy was performed to assess the position of stent and complications that occurred. Subsequent monitoring is adjusted to the underlying disease. Nebulization with normal saline is recommended to maintain airway hydration and prevent mucus plugs and secondary infection due to impaired airway clearance function after stent placement. Corticosteroids and antibiotics are recommended for 3–4 days after stent placement.[6,10]

Balloon Dilatation

Evaluation bronchoscopy was performed for inspection and measurement, and then serial dilation was performed with a larger bronchoscope. The blunt tip Jackson bronchoscope reduces mucosal trauma and the risk of tracheal or bronchial perforation. The procedure is repeated by using a larger bronchoscope until an adequate airway calibre is achieved. If the lesson narrows for applying the 3.5 mm Jackson bronchoscope, esophageal bougies (flexible Jackson) are used to enlarge the airway or bronchoscopic dilatation. Pneumatic or hydrostatic pressure balloon dilation angioplasty is used occasionally. If a dilation is greater than 8–9 mm, dilation bronchoscopy is required (Figure 4). [6,8,9,15]

Core-out

At the time of initial examination, the intraluminal mass was assessed to determine tumor size and distal tracheal anatomy. A bronchoscope is used to compress the mass to maintain airway patency and evaluate the extent of pathological lesions. Mechanical removal of the tumor was performed with a rigid bronchoscope tip and continued debridement with biopsy forceps. Control bleeding with suction periodically. If the bleeding does not stop, laser and cryotherapy may be performed.[1,4,9]

Laser ablation

Benign endobronchial tumors are sometimes subjected to laser procedures according to multidisciplinary joint decision. Laser vaporization is performed for residual endobronchial tumors after mechanical core-out, tumors that are not amenable to mechanical debridement, and airway granulation management.[16] An Nd: YAG laser (MBB-AT Medilas 2 Nd: YAG 621, MBB-Angewandte, Munich, Germany) was used with a power setting of 35 watts and a pulse duration of 0.5 seconds.[9,14,17]

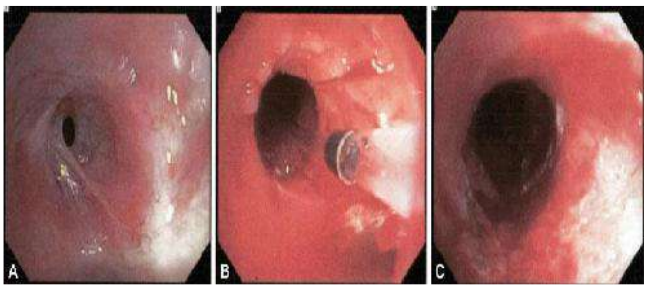

Figure 4. Granulomatosis polyangiitis (GPA) patient: (A) Bronchoscopic view of severe stenosis of the left main bronchus, (B) Post-treated airways with a radial cut followed by balloon dilation, (C) Left main bronchus diameter was significantly widened after ballooning dilation.[6]

CONCLUSION

Central airway obstruction is a respiratory emergency that requires immediate management. Benign central airway obstruction caused by infection, extrinsic compression, benign endobronchial tumors and dynamic airway wall abnormalities. Management requires a joint decision of multidisciplinary including pulmonary intervention, thoracic surgery, anesthesiologist and radiology. Bronchoscopy is a diagnostic and therapeutic modality for managing benign central airway obstruction and treating the underlying disease. Therapeutic bronchoscopy for managing benign central airway obstruction includes balloon dilatation, stent and laser.

REFFERENCES

1. Mitchell PD, Kennedy MP. Bronchoscopic management of malignant airway obstruction. Adv Ther. 2014;31(5):512–38.
2. Lawrence DA, Branson B, Oliva I, Rubinowitz A. The wonderful world of the windpipe: a review of central airway anatomy and pathology. Can Assoc Radiol J J Assoc Can Radiol. 2015;66(1):30–43.
3. Murgu SD, Egressy K, Laxmanan B, Doblare G, Ortiz-Comino R, Hogarth DK. Central Airway Obstruction: Benign Strictures, Tracheobronchomalacia, and Malignancy-related Obstruction. Chest. 2016;150(2):426–41.
4. Alraiyes AH, Machuzak MS. Rigid Bronchoscopy. Semin Respir Crit Care Med. 2014;35(6):671–80.
5. Oberg CL, Holden VK, Channick CL. Benign Central Airway Obstruction. Semin Respir Crit Care Med. 2018;39(6):731–46.
6. Holden VK, Channick CL. Management of benign central airway obstruction. AME Med J. 2018;3:76–76.
7. Buitrago DH, Wilson JL, Parikh M, Majid A, Gangadharan SP. Current concepts in severe adult tracheobronchomalacia: evaluation and treatment. J Thorac Dis. 2017;9(1):E57–66.
8. Kim H. ES 07.03 Bronchoscopic Management of Central Airway Obstruction. J Thorac Oncol. 2017;12(11):S1626–7.
9. Batra H, Yarmus L. Indications and complications of rigid bronchoscopy. Expert Rev Respir Med. 2018;12(6):509–20.
10. Chen DF, Chen Y, Zhong CH, Chen XB, Li SY. Long-term efficacy and safety of the Dumon stent for benign tracheal stenosis: a meta-analysis. J Thorac Dis. 2021;13(1):82–91.

11. Oda N, Sakugawa M, Hosokawa S, Fukamatsu N, Bessho A. Successful Long-term Management of Two Cases of Moderate Hemoptysis Due to Chronic Cavitary Pulmonary Aspergillosis with Bronchial Occlusion Using Silicone Spigots. Intern Med. 2018;57(16):2389–93.
12. Xu J, Ong HX, Traini D, Byrom M, Williamson J, Young PM. The utility of 3D-printed airway stents to improve treatment strategies for central airway obstructions. Drug Dev Ind Pharm. 2019;45(1):1–10.
13. Ayub A, Al-Ayoubi AM, Bhora FY. Stents for airway strictures: selection and results. J Thorac Dis. 2017;9(Suppl 2):S116–21.
14. Dalar L, Abul Y. Safety and Efficacy of Oki Stenting Used to Treat Obstructions in the Right Mainstem Bronchus. J Bronchol Interv Pulmonol. 2018;25(3):212–7.
15. Fang Y, You X, Sha W, Xiao H. Bronchoscopic balloon dilatation for tuberculosis-associated tracheal stenosis: a two case report and a literature review. J Cardiothorac Surg. 2016;11(1):21.
16. Elhidsi M, Zaini J, Ghanie A, Huswatun AL, Beginta R, Mety SH, et al. Therapeutic bronchoscopy followed by sequential radiochemotherapy in the management of life-threatening tracheal adenoid cystic carcinoma: a case report. J Med Case Reports. 202216(1):243.
17. Lee BR, Oh IJ, Lee HS, Ban HJ, Kim KS, Kim YI, et al. Usefulness of Rigid Bronchoscopic Intervention Using Argon Plasma Coagulation for Central Airway Tumors. Clin Exp Otorhinolaryngol. 2015 Dec;8(4):396–401.

Literature Review

Mesenchymal Stem Cells Role in COVID-19 Myocardial Injury

Triya Damayanti,[1] Mega Juliana,[1] Yasmina Hanifah,[2] Erlina Burhan,[1] Putri Suci Ramadhany[3]

[1] Department of Pulmonology and Respiratory Medicine of Universitas Indonesia/ RSUP Persahabatan, Jakarta, Indonesia
[2]Heart and Vascular Medical Staff Group, RSUP Persahabatan, Jakarta, Indonesia
[3]Faculty of Medicine, Nursing and Health Sciences, Monash University, Australia

Abstract

Coronavirus Disease-19 (COVID-19) has become a global pandemic that affected the lives of billion individuals. The clinical spectrum of the disease varies from asymptomatic form to severe manifestation in term of acute respiratory distress syndrome (ARDS), shock and septic shock and multiple organ dysfunction syndrome (MODS). Clinical studies have also reported an association between COVID-19 and cardiovascular manifestation, such as myocardial injury, arrhythmias, acute coronary syndrome (ACS) and thromboembolism. Myocardial injury has been reported frequently and is associated with high mortality. The currently approved strategies for COVID-19 are supportive rather than curative treatment. Cell-based approaches, primarily using mesenchymal stem cell (MSC) has demonstrated safety and possible efficacy as an adjuvant therapy in COVID-19 patient. Mesenchymal stem cells have shown important role in the therapy of cardiovascular disease due to their prominent features including their ability to differentiate into cardiovascular cells, immunomodulatory properties, antifibrotic activity and ability to undergo neovasculogenic.

Keywords: COVID-19, mesenchymal stem cell, myocardial injury

Corresponding Author:
Triya Damayanti | Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan Hospital, Jakarta, Indonesia | tria_94@yahoo.com

Submitted: May 21st, 2021
Accepted: February 4th, 2022
Published: October 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 4: 347–53
https://doi.org/10.36497/jri.v42i4.192

INTRODUCTION

COVID-19 pneumonia began with the start of pneumonia epidemic of unknown etiology in Wuhan city, China at the end of 2019. Epidemiological surveillance showed that the case was related to seafood market in Wuhan. In 7th January 2020, Chinese government announced that the epidemic was caused by a new strain of coronavirus, which was in the same family with the viruses causing severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), therefore named SARS-CoV-2. SARS-CoV-2 is more virulent and easier to spread, and status of pandemic was declared in 11th March 2020.[1]

SARS-CoV-2 infection will activate natural and cellular immune response. In COVID-19, excessive immune response called 'cytokine storm' may occur, causing severe to critical clinical manifestation. Cytokine storm will cause acute respiratory distress syndrome (ARDS) and multiorgan failure. After binding to ACE2 receptor, SARS-CoV-2 will invade respiratory tract epithelium. Dendritic cells and alveolar macrophages activated by SARS-CoV-2 entry will release interleukin-6 (IL-6) which is also secreted by epithelial cells in respiratory tract. Interleukin-6 (IL-6) will induce the release of some acute phase proteins such as CRP, D-dimer and ferritin, and other proinflammatory cytokines like IL-1B, IL-12, TNF-α. These cytokines will induce leukocyte to releasse other proinflammatory cytokines, which aggravate the ongoing inflammation process.[2]

MYOCARDIAL INJURY IN COVID-19

Myocardial injury is the most common cardiovascular manifestation found in COVID-19 pneumonia. Prevalence of myocardial injury in COVID-19 pneumonia reported by some studies was 5–20%, and higher in severe and critical degree of disease, reaching 44%.[3] Meta-analysis by Zou F et

al reported 24,4% prevalence of myocardial injury in admitted patients with increased mortality rate 5 times higher compared to those without myocardial injury.[3] Shao MJ et al reported 5,9 times increase of mortality rate in COVID-19 pneumonia patients with myocardial injury compared to those without myocardial injury.[4]

Myocardial injury is defined as an increase in cardiac Troponin I (cTnI) level in blood above 99th percentile from upper range of normal values. Myocardial injury can occur in acute or chronic duration.[4–8] Cardiac troponin I and troponin T are the component of contractile apparatus in cardiac muscle cells, secreted almost exclusively in myocardial muscle cells. Increase of troponin I was reported to not occur in injuries other than myocardial cells, however, troponin T was also reported to increase in skeletal muscle injury. Therefore, troponin I has high sensitivity and is a recommended routine evaluation.[8]

Cardiac troponin is located intracellular, with more than 90% found in sarcomeres, unbound in cytoplasm. Cardiac troponin can be released in the circulation in the situation of myocyte necrosis, apoptosis, form and release of bleb in membrane, increase of membrane permeability and release of degradation product of proteolytic troponin. Moreover, mechanism outside the heart may also induce troponin release without myocyte necrosis, some of which are mechanical stretch in overload condition inducing activation of intracellular protease related to intracellular troponin degradation, condition of tachyarrhythmia stimulating stress response in cardiomyocyte causing troponin release from viable cardiomyocyte cells and in diseases with proinflammatory and prothrombotic environment causing platelet aggregation to thromboembolism.[5]

Table 1. Cause of Troponin Increase

Ischemic Myocardial Injury	Myocardial Ischemic Injury due to Imbalance of Oxygen Supply and Demand	Other Causes
Atherosclerotic plaque rupture or thrombosis	Decreased myocardial perfusion caused by: Coronary artery spasm, microvascular disfunction 1. Coronary embolism 2. Coronary artery dissection 3. Persistent bradyarrhythmia 4. Hypotension or shock 5. Respiratory failure 6. Severe anemia	Cardiac diseases: 1. Heart failure 2. Myocarditis 3. Cardiomyopathy 4. Coronary revascularization procedure 5. Catheter ablation 6. Defibrillation shock 7. Heart contusion
	Increase of myocardial oxygen demand, caused by: 1. Persistent tachyarrhythmia 2. Severe hypertension with or without left ventricle hypertrophy	Systemic problems: 1. Sepsis, infectious disease 2. Chronic kidney disease 3. Stroke 4. Lung embolism, pulmonary hypertension

Myocardial injury is a precondition for myocardial infarct diagnosis, but can also be its own entity due to etiologies other than ischemic process. Myocardial infarct is defined pathologically as death of myocardial muscle cells due to long term ischemic process. In the beginning of ischemic onset, structural changes that happen are damage of cellular glycogen, relaxing myofibrils, damage of sarcolemma structure and abnormality of mitochondria, while the death of myocardial muscle cells need a few hours. Myocardial injury can correlate to ischemic or non-ischemic process with various underlying condition (Table 1).[9]

Another biomarker that may be released by the myocardium during insult is N-terminal pro-brain natriuretic (NT proBNP). Some studies have investigated its role in myocardial manifestation in COVID-19. Troponin I and NT proBNP are important prognostic factors in COVID-19 patients. NT proBNP is a molecule secreted by myocardial muscle cells as a response towards mechanical stretch due to volume overload or ventricular volume overload. NT

proBNP is a quantitative biological marker of hemodynamic stress and heart failure that often increases in patients with inflammatory disease and/or severe breathing. In the condition of acute heart ischemia, BNP level increase in proportion to the degree of left ventricle dysfunction. In the event of acute myocardial infarcts, NT proBNP level may increase along with other myocardial injury markers such as troponin T, CKMB and myoglobulin. Gao L et al reported high NT proBNP level as death predictor in hospital stay for COVID-19 pneumonia patients.[10] Meta-analysis by Pranata R et al. reported that high NT proBNP level increases risk of death with 1.37 hazard ratio.[11]

PATHOGENESIS OF MYOCARDIAL INJURY IN COVID-19

ACE2 receptors as the entry point of SARS-COV-2 are also expressed a lot in the heart and vessels. ACE2 is a part of renin-angiotensin-aldosterone system (RAAS) involved in the development of hypertension, heart failure and diabetes. ACE converts angiotensin I into angiotensin II. Angiotensin II is the main effector molecule in RAAS. ACE2 will convert angiotensin II into angiotensin 1-7. Angiotensin II level increases in various pathological conditions, hence ACE2's protective properties in cardiovascular system. In SARS-COV-2 infection, it is thought that decreasing ACE2 level intermediate the process of disorder in the cardiovascular system.[6]

Cardiovascular manifestations in COVID-19 generally include myocardial injury, arrhythmia, acute coronary syndrome (ACS), thromboembolism, to heart failure and cardiac arrest. Mechanism of myocardial injury in COVID-19 pneumonia has not been fully understood. Some possible mechanisms include:[12,13]

1. Directly causing myocardial injury

   The binding of SARS-COV-2 with ACE2 in the heart will cause changes in heart signaling pathway, causing acute injury of heart muscles, lung muscles, as well as microvascular and macrovascular dysfunction.

2. Systemic inflammation

   In COVID-19 with severe to critical symptoms, excessive systemic inflammatory response occurs (cytokine storm). Cytokine storm causes multiorgan injury or even multiorgan failure, including in cardiovascular system. Furthermore, T cell and activated macrophages are thought to be able to infiltrate myocardium, causing fulminant myocarditis to severe heart damage. Severe systemic inflammation also causes increasing cardiometabolic demand due to hypoxia. This will change demand and supply ratio that further will cause myocardial injury.

3. Plaque rupture and coronary thrombosis

   Systemic inflammation also causes an increase in coronary blood flow along with hypercoagulable intravascular environment, resulting in unstable and easily ruptured atherosclerotic plaque, causing acute myocardial infarct.

4. Adverse effect of therapy

   Several antiviral medicines, quinine pills, corticosteroid and other medicines for COVID-19 management may cause adverse effects that affect cardiovascular system.

ECG FINDINGS IN COVID-19

Until recently, there is no specific changes of ECG finding in patients with COVID-19 pneumonia, therefore it is thought that the damage in myocardial cells is minimal and doesn't cause specific ECG changes in most patients, although ST-elevation finding in myocarditis patient has been reported. Therefore, ECG diagnostic criteria in COVID-19 pneumonia is no different with any other heart diseases. One publication on 138 COVID-19 patients reported 16.7% arrhythmia cases and 44.4% in 16 ICU admitted patients, but the association between COVID-19 and arrhythmia had not been clearly known.[13]

ECHOCARDIOGRAPHY FINDINGS IN COVID-19

Echocardiography is not an established practice for COVID-19 patients. Skezely et al. evaluated 100 COVID-19 patients and found no abnormalities of basic examination in 32% patients. The most common abnormalities were dilatation and dysfunction of right ventricle (39%), diastolic dysfunction of left ventricle (16%), and systolic dysfunction of left ventricle (10%). Increase of troponin level is reported to be linked with decreasing right ventricle function and deteriorating clinical symptoms.[14]

CARDIOVASCULAR COMORBIDITIES IN COVID-19

Cardiovascular disease is a comorbidity often found in SARS and MERS (with 10% and 30% prevalence), as well as in COVID-19 pneumonia. The most common cardiovascular comorbidities in COVID-19 pneumonia are hypertension and diabetes mellitus. Some studies in China reported different prevalence of cardiovascular comorbidities in COVID-19 pneumonia, ranging from 2.5% to 15%. Meanwhile, report in America showed 11–14% prevalence, and 21% in Italy. The number of prevalence is reported higher in patients with severe and critical disease. China CDC reported overall mortality rate of 2.3% in China, but mortality rate for COVID-19 with cardiovascular comorbidity increased up to 10.5%.[6]

MESENCHYMAL STEM CELLS THERAPY IN COVID-19

Mesenchymal stem cell is introduced as one of adjuvant managements in COVID-19 pneumonia that is currently investigated abroad. In the last 20 years, studies about mesenchymal stem cell reported its safety for use and good tolerability. Leng et al reported that mesenchymal stem cell administration in COVID-19 patients improved patient's outcome with no report of serious adverse effects.[15] Zhang et al reported increase of CD3+, CD4+ and CD8+ cells and decrease of IL-6, CRP and TNF-α levels after administration of mesenchymal stem cell therapy.[16] Liang et al reported that mesenchymal stem cell administration is well tolerated and shows improvement of clinical condition and biological markers.[17]

Mesenchymal stem cell is a multipotent mature non hematopoietic stem cell with characteristic ability to self-renew and differentiate in mesodermal pathway (osteocyte, adipocyte and chondrocyte), ectodermal (neurocyte) and endodermal (hepatocyte). Mesenchymal stem cell is currently able to be isolated from various structures, such as adipose tissue, amniotic fluid and membrane, teeth tissue, peripheral blood cells, placenta and fetal membrane, salivary gland, skin, sub amniotic umbilical membrane and synovial fluid.[18] Mesenchymal stem cell offers multiple advantages, such as being easily obtained and cultured, multipotent, ability to be stored for repetitive administration of therapy, no reported serious adverse effects, and available report of efficacy from multiple prior clinical research.[19]

Mesenchymal stem cell has the potential as immunomodulator, proangiogenic, anti-apoptosis and having a role in tissue repair. Its role as an immunomodulator is crucial in reducing inflammatory response leading to ARDS in COVID-19. Mesenchymal stem cell can increase polarization of monocyte or M2 phenotype macrophage which serves as antiinflammation and inhibits proliferation and differentiation of T cells, thus suppressing inflammation process. Anti-inflammatory monocyte will secrete large amount of IL-10 mediated by IL-6 and *hepatocyte growth factor* (HGF). IL-10 will inhibit differentiation of monocyte into dendritic cells and induce monocytes into anti-inflammatory monocyte. Mesenchymal stem cell will also release prostaglandin E2 (PGE2) that induces macrophage to release anti-inflammatory cytokines and activate regulatory cell (T reg) thus inhibiting proliferation and activation of effector T cell, resulting in decrease of endothelium and alveolar epithelium permeability.[20–24]

On the other hand, mesenchymal stem cell will express class II MHC, CD45R dan CD11b that will suppress the activity of T cells. Monocyte will induce formation of T reg cells, mediated by CCL-18 and

transforming growth factor-β1 (TGF-β1). CCL-18 will inhibit CD4+CD25- effector T cell proliferation. Effector T cell proliferation is also inhibited by mesenchymal stem cell mediated by TGF-β1, IDO and galectin. Mesenchymal stem cell is also responsible for intra-alveolar fluid clearance when ARDS occurs by ventoral transport in alveolar epithelial cells done by fibroblast growth factor-7 (FGF-7). [20–24]

Mesenchymal stem cell is administered through injection or inhalation. Mesenchymal stem cell administered with injection will be contained in lung capillaries. Then, it will improve the microenvironment in lung tissues, protect alveolar epithelial cells, decrease pulmonary fibrosis and lessen lung disfunction. In studies with lab animals, mesenchymal stem cell will be phagocytosed by monocyte or macrophage. Phagocytosis will cause changes of monocyte or macrophage properties into monocyte with type 2 phenotype, which is immunosuppressive. Accumulated immunosuppressive monocyte or macrophages will be distributed to neighboring tissue and undergo its role to suppress inflammatory response. Recommended dosage of mesenchymal stem cell administration is 0.5×10^6 to 1×10^7 cells/kgBW.[18,19,24]

ROLE OF UMBILICAL CORD MESENCHYMAL STEM CELLS IN MYOCARDIAL INJURY

Mesenchymal stem cell has an important role in cardiovascular disease. Mesenchymal stem cell has the ability to differentiate into cardiovascular cells, as an immunomodulator, antifibrotic and increase neovasculogenesis. Extracellular vesicle of mesenchymal stem cell is also able to mediate some cellular functions, such as increasing cardiomyocyte autophagic ability through HIF-1α/Jagged-1 pathway, decreasing cell apoptosis and activating pathway for cell survival through multiple microRNA (miRs). Currently, approaches have been implemented to increase therapeutic ability of mesenchymal stem cell, including genetic modification and combination with other biological agents.[25]

After implantation, mesenchymal stem cell will be distributed in myocardial tissue zone that is similar with cardiomyocyte cells. Increase of specific markers for myocardium such as troponin T, will affect mesenchymal stem cell differentiation into cardiomyocyte cells. Administration of *basic fibroblast growth factor* (bFGF) through coronary vein is able to increase differentiation of mesenchymal stem cell phenotypes into cardiomyocyte, maintain heart function and prevent poor remodeling. Moreover, mesenchymal stem cell can genetically induce itself into *cardiomyocyte-like cell*.[25]

When myocardial injury occurs, monocyte migrate to location of the injury and differentiate into macrophages in the tissue. Macrophage will then secrete cytokines, chemokines and growth factor that facilitates in suppressing process of injury or ongoing myocardial infarct. Macrophage will further differentiate into M1 and M2. M1 macrophage will release interferon, *tumor necrosis factor* (TNF) and IL-23 which has proinflammatory properties, while M2 macrophage has anti-inflammatory role by increasing cell proliferation and angiogenesis that regulate ongoing inflammatory process.[25]

Through study on experimental animals, Miteva et al. reported that mesenchymal stem cell administration will decrease the severity of myocarditis and the number of proinflammatory monocyte, while increase of Ly6C levels secreted by anti-inflammatory monocytes also occurs in the blood, heart, and spleen of experimental animals.[26] Chiossone et al reported that mesenchymal stem cell could increase polarization of macrophage differentiation into M2 through a pathway that requires prostaglandin and inhibit T cell proliferation. Mesenchymal stem cell interaction with macrophage will increase expression of CD206 and IL-10 in vitro that serves as anti-inflammatory cytokines.[27]

Myocardial fibrosis occurs following myocardial injury. Myocardial fibrosis is marked by excessive collagen deposit in heart muscle. This causes stiffening of heart muscle, therefore decreasing systolic and diastolic function, and scar may form on heart muscle. Heart muscle cells undergoing necrosis in the infarcted area will be replaced by

fibroblast tissue that may cause ventricle remodeling, arrhythmia, and even death. Mesenchymal stem cell is able to regulate matrix metalloproteinase which inhibits fibroblast activation and decreases extracellular matrix deposit.[25]

Clinical study of mesenchymal stem cell in cardiovascular disease was first conducted by Hare J at United Kingdom in 2005. This study included myocardial infarct patients and reported good safety profile and mesenchymal stem cell efficacy.[28] Another study with similar result was reported by Ankara university in 2015 by administering umbilical cord mesenchymal stem cell in chronic ischemic cardiomyopathy patients.[29]

CONCLUSION

Myocardial injury is the most common cardiovascular manifestation in COVID-19 pneumonia patients. Mortality rate of COVID-19 pneumonia patients with myocardial injury increases by 5.9 times compared to no myocardial injury. Myocardial injury in COVID-19 may occur in some possible mechanisms; directly causing myocardial injury, systemic inflammation, plaque rupture and coronary thrombosis and adverse effect of therapy. Mesenchymal stem cell has the potential as immunomodulator, proangiogenic, anti-apoptosis and plays a role in tissue repair. Its role as immunomodulator can be a promising alternative therapy to resolve myocardial injury. Nevertheless, further research is needed to understand cellular and molecular function that take part in interactions between mesenchymal stem cell, cardiomyocyte and occurring immune response. Clinical trial with large sample is needed to obtain characteristic risk-benefit profile of mesenchymal stem cell use, in order to make appropriately targeted selection of adjuvant therapy in COVID-19.

REFFERENCES

1. Kementerian Kesehatan RI. Pedoman Pencegahan dan Pengendalian Coronavirus Disease (COVID-19). Indonesia; Revisi ke-5, 2020.
2. Cao Z, Jia Y, Zhu B. BNP and NT-proBNP as diagnostic biomarkers for cardiac dysfunction in both clinical and forensic medicine. Int J Mol Sci. 2019;20(8):1820.
3. Zou F, Qian Z, Wang Y, Zhao Y, Bai J. Cardiac injury and COVID-19: A systematic review and meta-analysis. CJC Open. 2020;2(5):386–94.
4. Shao MJ, Shang LX, Luo JY, Shi J, Zhao Y, Li XM, et al. Myocardial injury is associated with higher mortality in patients with coronavirus disease 2019: a meta-analysis. J Geriatr Cardiol. 2020;17(4):224–8.
5. K AB, Chaudhuri D. A review of acute myocardial injury in coronavirus disease 2019. Cureus. 2020;12(6).
6. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543–58.
7. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation. 2020;141(20):1648–55.
8. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Circulation. 2018;138(20):e618–51.
9. Gatta F, Dolan C. Acute myocardial injury in COVID-19: Epidemiology, aetiology and management. Cardiol Cardiovasc Med. 2020;4(4):283–91.
10. Gao L, Jiang D, Wen XS, Cheng XC, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res. 2020;21(1):83.
11. Pranata R, Huang I, Lukito AA, Raharjo SB. Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: Systematic review and meta-analysis. Postgrad Med J. 2020;96(1137):387–91.
12. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: Implications for

risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116(10):1666–87.
13. Baigent C, Windecker S, Andreini D, Arbelo E, Barbato E, Bartorelli AL, et al. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1—epidemiology, pathophysiology, and diagnosis. Eur Heart J. 2022;43(11):1033–58.
14. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, et al. Spectrum of cardiac manifestations in COVID-19: A systematic echocardiographic study. Circulation. 2020;142(4):342–53.
15. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2 mesenchymal stem cell improves the outcome of patients with COVID-19 pneumonia. Aging Dis. 2020;11(2):216–28.
16. Zhang Y, Ding J, Ren S, Wang W, Yang Y, Li S, et al. Intravenous infusion of human umbilical cord Wharton's jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia. Stem Cell Res Ther. 2020;11(1):1–6.
17. Liang B, Chen J, Li T, Wu H, Yang W, Li Y, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report. Medicine. 2020;99(31):E21429.
18. Ullah I, Subbarao RB, Rho GJ. Human mesenchymal stem cells - current trends and future prospective. Biosci Rep. 2015;35(2):e00191.
19. Golchin A, Seyedjafari E, Ardeshirylajimi A. Mesenchymal stem cell therapy for COVID-19: Present or future. Stem Cell Rev Rep. 2020;16(3):427–33.
20. Weiss ARR, Dahlke MH. Immunomodulation by mesenchymal stem cells (MSCs): Mechanisms of action of living, apoptotic, and dead MSCs. Front Immunol. 2019;10:1191.
21. Horie S, Gonzalez HE, Laffey JG, Masterson CH. Cell therapy in acute respiratory distress syndrome. J Thorac Dis. 2018;10(9):5607–20.
22. Atluri S, Manchikanti L, Hirsch JA. Expanded umbilical cord mesenchymal stem cell (UC-MSC) as a therapeutic strategy in managing critically ill COVID-19 patients: The case for compassionate use. Pain Physician. 2020;23(2):E71–83.
23. Saldanha-Araujo F, Melgaço Garcez E, Silva-Carvalho AE, Carvalho JL. Mesenchymal stem cells: A new piece in the puzzle of COVID-19 treatment. Front Immunol. 2020;11:1563.
24. Jimenez-Puerta GJ, Marchal JA, López-Ruiz E, Gálvez-Martín P. Role of mesenchymal stromal cells as therapeutic agents: Potential mechanisms of action and implications in their clinical use. J Clin Med. 2020;9(2):445.
25. Guo Y, Yu Y, Hu S, Chen Y, Shen Z. The therapeutic potential of mesenchymal stem cells for cardiovascular diseases. Cell Death & Disease. 2020;11(5):1–10.
26. Miteva K, Pappritz K, El-Shafeey M, Dong F, Ringe J, Tschöpe C, et al. Mesenchymal stromal cells modulate monocytes trafficking in coxsackievirus B3-induced myocarditis. Stem Cells Transl Med. 2017;6(4):1249–61.
27. Chiossone L, Conte R, Spaggiari GM, Serra M, Romei C, Bellora F, et al. Mesenchymal stromal cells induce peculiar alternatively activated macrophages capable of dampening both innate and adaptive immune responses. Stem Cells. 2016;34(7):1909–21.
28. Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. J Am Coll Cardiol. 2009;54(24):2277–86.
29. Can A, Ulus AT, Cinar O, Topal Celikkan F, Simsek E, Akyol M, et al. Human umbilical cord mesenchymal stromal cell transplantation in myocardial ischemia (HUC-HEART Trial). A study protocol of a phase 1/2, controlled and randomized trial in combination with coronary artery bypass grafting. Stem Cell Rev Rep. 2015;11(5):752–60.

AUTHORS INDEX

SUBJECTS INDEX