VOL. 42, NO. 1, January 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

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 1, January 2022

TABLE OF CONTENT

Original Article

Respiratory Emergency in Hospitalized patient with Intrathoracic Malignancy at H. Adam Malik General Hospital

Elizabeth Napitupulu[1], Noni Novisari Soeroso[1], Setia Putra Tarigan[1], Putri Chairani Eyanoer[2]

[1]Department of Pulmonology and Respiratory Medicine Faculty of Medicine, University of Sumatera Utara, Medan
[2]Institute for Research and Community Development Service, University of Sumatera Utara, Medan

Abstract

Background: *Increased number of intrathoracic malignancy cases (Lung tumor, Mediastinum tumor, Secondary lung cancer and Chest wall tumor) contribute in increased complications of respiratory emergencies such as superior cava vein yyndrome (scvs), massive malignant pleura effusion (mpe), central airway obstruction (cao), massive hemoptysis, lung thromboembolism and pneumothorax. This study aims to look at the proportions, outcomes, and factors that influence respiratory emergency in intrathoracic malignancy cases.*
Methods: *This was a retrospective case series of inpatient respiratory emergencies in patients intrathoracic malignancy at H. Adam Malik Central General Hospital - Medan from 1 May 2011 to 30 April 2016.*
Results: *From 690 subjects intrathoracic malignancy, there were 137 (19.8%) patients with respiratory emergencies and mostly caused by lung tumors (83.9%). Massive MPE was is the most common emergency of 45 cases (6.5%) and massive haemoptysis of at least 4 cases (0.6%). The risk of death was higher in patients with respiratory emergencies. Mediastinum and location of tumor contribute in respiratory emergency appearance with respective OR of 3.9 and 1.5 (p value <0.005)*
Conclusions: *Increased of mortality rate in patients with respiratory emergency and MPE massive is the most cases. Type of the malignancy and Right lung tumor contribute of respiratory emergency in intrathoracic malignancy cases. (**J Respirol Indones 2022; 42(1): 1–8)***
Keywords: *respiratory emergency, intrathoracic malignancy, incidence, outcome*

Kegawatdaruratan Respirasi pada Pasien Rawat Inap dengan Keganasan Intratoraks di RSUP H. Adam Malik

Latar belakang: *Meningkatnya kasus keganasan rongga toraks (Tumor paru, Tumor mediastinum, Tumor paru metastase dan Tumor dinding dada) menyebabkan meningkatnya komplikasi berupa kegawatdaruratan respirasi seperti Sindroma vena kava superior (SVKS), Efusi pleura ganas (EPG) Masif, Central airway obstruction (CAO), Hemoptisis masif, Tromboemboli paru dan Pneumotoraks. Penelitian ini bertujuan untuk melihat proporsi, luaran, dan faktor yang mempengaruhi munculnya kegawatdaruratan respirasi pada keganasan rongga toraks.*
Metode Penelitian: *Penelitian ini merupakan laporan kasus serial yang dilakukan secara retrospektif terhadap kasus kegawatdaruratan respirasi pada pasien keganasan rongga toraks yang dirawat inap di RSUP H. Adam Malik Medan pada periode 1 Mei 2011 – 30 April 2016.*
Hasil: *Dari 690 subjek dijumpai sebanyak 137 (19.8%) dengan kegawatdaruratan respirasi dan penyebab terbanyak adalah tumor paru (83.9%). Efusi pleura ganas masif merupakan kegawatdaruratan terbanyak yaitu 45 kasus (6.5%) dan hemoptisis masif yang paling sedikit 4 kasus (0.6%). Risiko kematian lebih tinggi pada pasien dengan kegawatdaruratan respirasi. Tumor mediastinum dan tumor paru kanan lebih berisiko menimbulkan kegawatdaruratan respirasi dengan OR masing - masing 3.9 dan 1.5 (p-value <0.05)*
Kesimpulan: *Meningkatnya angka kematian pada pasien dengan kegawatdaruratan respirasi dan didominasi kasus EPG masif. Jenis keganasan dan letak tumor di kanan berpengaruh terhadap munculnya kegawatdaruratan respirasi. (**J Respirol Indones 2022; 42(1): 1–8)***
Kata kunci: *kegawatdaruratan respirasi; keganasan rongga toraks; angka kejadian; luaran*

Correspondence: Elizabeth Napitupulu
Email: napitupuluelizabeth@gmail.com

INTRODUCTION

Intrathoracic malignancy consists of lung cancer, mediastinal tumors, mesothelioma, secondary lung tumors and chest wall tumors.[1] Respiratory emergencies are one of the oncology emergencies due to complications or adverse reaction of the treatment that requires prompt immediate action to prevent death or serious organ damage.[2]

Lung cancer is a malignant disease with high mortality rate and the most cause of death due to cancer in the United States with 5 years survival rate only 17.7%.[3] Increase number of lung cancer and intrathoracic malignancy lead to increase oncology emergency cases especially respiratory emergencies. Minami et al, conducted a study of 245 lung cancer patients who came to the Emergency Room (ER) and found that respiration complaints were the most cases (37.6%).[4]

Respiratory emergency is a life-threatening condition, and require immediate attention due to disruption of gas exchange in the lung or failure of the respiratory system, which if it is not addressed immediately can lead to a condition called acute respiratory failure characterized by declining oxygen in the arteries (hypoxemia) or elevated levels of carbon dioxide (hypercarbia) or a combination of both. Respiratory emergency due to malignancy such as Superior vena cava syndrome (SVCS), malignant pleural effusion (MPE), massive hemoptysis, venous thromboembolism (deep vein thrombosis and pulmonary embolism), central airway obstruction (CAO) and pneumothorax.[5]

From previous studies found that the incidence of Massive pleural effusion about 11.2% of all pleural effusions and 53.7% caused by malignancy.[6] While the incidence SVCS about 3.8%, CAO as much as 13%, Venous thromboembolism 21%, Massive hemoptysis 3%, and pneumothorax was found as much as 0.03–0.05%.[7–11]

The risk of death will increase in patients intrathoracic malignancies with respiratory emergency. The aim of this study was to determine the proportions, outcomes, and factors that related to the respiratory emergencies in hospitalized intrathoracic malignancies patients.

METHOD

This study is a case series which was conducted retrospectively in intrathoracic malignancy patients with respiratory emergencies who were hospitalized at H. Adam Malik General Hospital in 5 years period (1st May 2011 to 30th April 2016).

The samples in this study are total sampling that fulfill the inclusion and exclusion criteria. The inclusion criteria were diagnosis of intrathoracic malignancy (lung tumor, mediastinal tumor, secondary lung tumor, chest wall tumor and mesothelioma) based on cytology or histopathology examination, and patients who were on treatment or not (e.g surgery, chemotherapy or radiotherapy). The exclusion criteria were patients with pulmonary tuberculosis or post tuberculosis, patients with blood clotting disorders and patients whose diagnose of malignancy was established from other hospital. The diagnosis of respiratory emergency based on the gold standard: (1) Massive MPE, defined by the present of malignant cells from pleural fluid examination on pleural biopsy with massive size of pleural effusion from CXR; (2) SVCS was diagnosed from clinical finding and Thoracic CT scan; (3) CAO was diagnosed by the presence of airway obstruction in the trachea or the main carina by bronchoscopy; (4) Massive hemoptysis, based on Bushro's criteria, is the discovery of bloody cough at least 600 mL/24 hours or bloody coughing <600 mL and ≥250 mL with Hb <10g% and still lasting 24 hours or bloody cough <600 mL and ≥250 mL with Hb >10g% and still continues within 48 hours;[12] (5) venous thromboembolism/pulmonary embolism, established from Ct angiography/VQ Scan and Well Score; (6) Pneumothorax was established clinically and radiologically.

All research procedures have been approved by the Health Research Ethical Commission. Data were obtained from the Medical Record Unit and data processing was performed

using the Statistical Package for Social Sciences (SPSS) where p value <0.05 was considered significant.

RESULTS

As much as 690 patients enrolled in this study from 5 years period. The characteristics of the subject (Table 1) mostly in age ranged between 50–59 years (38.4%), and male predominant (78.8%).

Majority of educational background was senior high school (50.4%) but mostly unemployed (47.5%). The proportion of intrathoracic malignancies found that lung tumors was the most cases about 626 cases (90.8%), mediastinal tumors 32 cases (4.6%) and secondary lung tumors as many as 32 cases (4,6%). While chest wall tumor and mesothelioma were not seen from the observation period. As many as 197 patients died during hospitalization and 493 patients discharge from hospital with outpatient treatment or by their own request.

Of the 690 cases of intrathoracic malignancy, 137 cases (19.8%) came with respiratory emergencies complication and 553 cases (80.2%) without respiratory emergency (Table 2). The distribution of respiratory emergencies every year can be seen in Figure.1, where the percentage of patients who present with respiratory emergencies is almost similar every year, with ranged 16.3% to 27.8%. The most common respiratory emergency was massive MPE about 45 cases (6.5%) followed by superior vena cava syndrome (svcs) (40; 5.8%), central airway obstruction (cao) (27; 3.9%), pneumothorax (11; 1.6%) and massive hemoptysis (4; 0.6%), which can be seen in Table 2. The annual distribution of respiration emergencies can be seen in Figure 2. In this study also found 10 (1.4%) patients who came with multiple emergencies (> 1 respiratory emergency) with annual distribution between 0–3.1%.

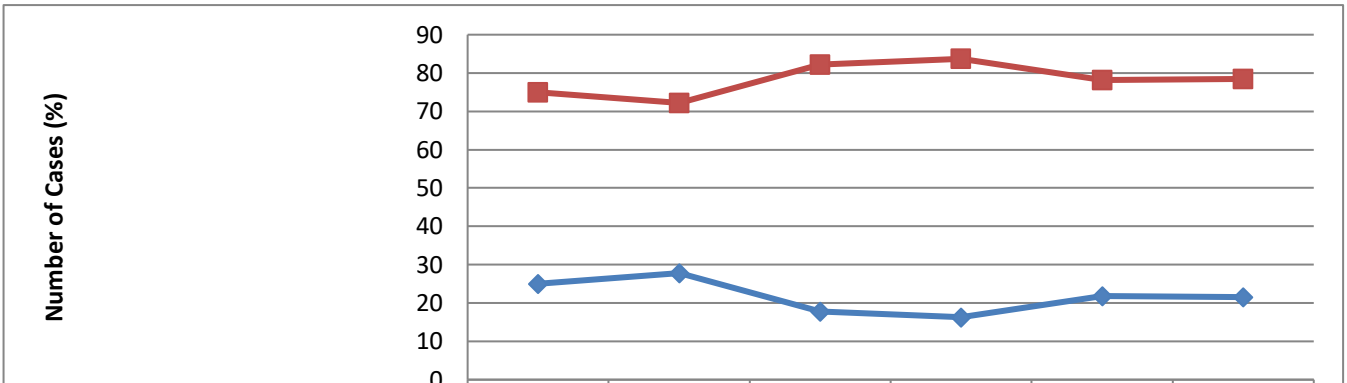
Table 1. Characteristic of Intrathoracic Malignancy Patients

Characteristic		n	%
Age (years)	<40	47	6.8
	40–49	120	17.4
	50–59	265	38.4
	60–69	186	27.0
	≥70	72	10.4
Gender	Female	146	21.2
	Male	544	78.8
Occupation	Civil Servant	49	7.1
	Private	313	45.4
	Unemployed	328	47.5
Education	Never school	1	0.1
	Primary School	152	22.0
	Middle High School	111	16.1
	Senior High School	348	50.4
	Diploma/Bachelor	78	11.3
Malignancy	Lung Tumor	626	90.7
	Mediastinal Tumor	32	4.6
	Secondary Lung Tumor	32	4.6
Outcome	Death	197	28.5
	Outpatient	493	71.5

Table 2. Distribution of Respiratory Emergency in Intrathoracic Malignancy Patient

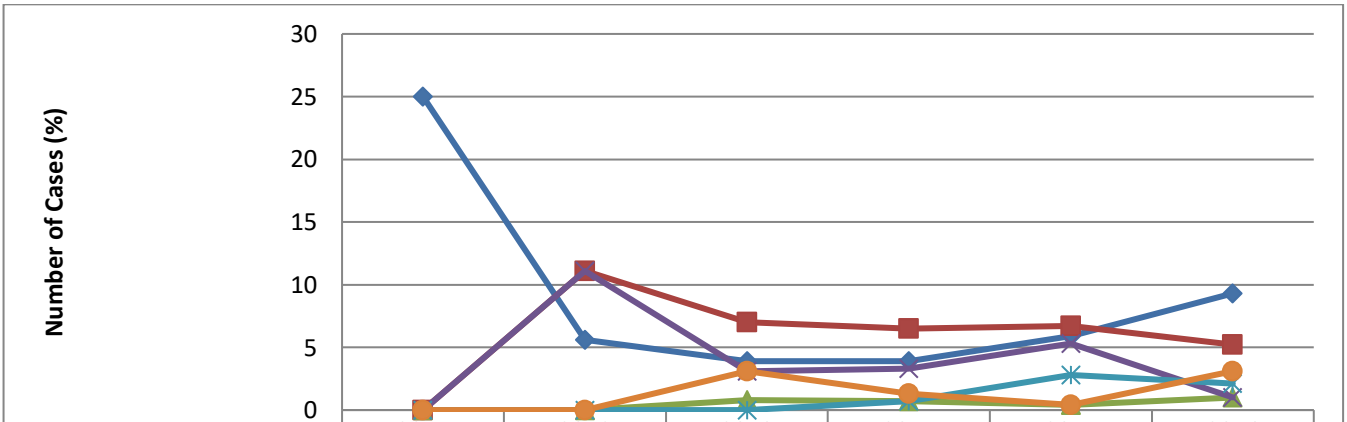
		2011		2012		2013		2014		2015		2016		SUM
		n	%	n	%	n	%	n	%	n	%	n	%	N (%)
Respiratory Emergency	With Respiratory Emergency	25	18.2	38	27.8	23	17.8	25	16.3	61	21.8	16	21.6	137 (19.8)
	Without Respiratory Emergency	66	11.9	13	72.3	106	82.2	128	83.7	224	78.2	76	78.4	553 (80.2)
Type of Respiratory Emergency	SVCS	25	18.2	11	5.6	5	3.9	6	3.9	17	5.9	9	9.3	40 (5.8)
	Massive MPE	0	0	21	11.1	9	7.0	10	6.5	19	6.7	5	5.2	45 (6.5)
	Massive Hemoptysis	0	0	0	0.0	1	0.8	1	0.7	1	0.4	1	1.0	4 (0.6)
	CAO	0	0	21	11.1	4	3.1	5	3.3	15	5.3	1	1.0	27 (3.9)
	Pneumothorax	0	0	0	0.0	0	0.0	1	0.7	8	2.8	2	2.1	11 (1.6)
	Multiple RE	0	0	0	0.0	4	3.1	2	1.3	1	0.4	3	3.1	10 (1.4)

Note: SVCS= Superior Vena Cava Syndrome, CAO = Central Airway Obstruction, RE=Respiratory Emergency



	2011	2012	2013	2014	2015	2016
Respiratory Emergency	25	27.8	17.8	16.3	21.8	21.6
Without Respiratory Emergency	75	72.2	82.2	83.7	78.2	78.4

Figure 1. Respiratory Emergency Chart from 2011–2016



	2011	2012	2013	2014	2015	2016
SVCS	25	5.6	3.9	3.9	5.9	9.3
Massive MPE	0	11.1	7	6.5	6.7	5.2
Massive Hemoptysis	0	0	0.8	0.7	0.4	1
CAO	0	11.1	3.1	3.3	5.3	1
Pneumothorax	0	0	0	0.7	2.8	2.1
Multiple RE	0	0	3.1	1.3	0.4	3.1

Figure 2. Distribution of Respiratory Emergency in 2011–2016

Table 3. Factors related to the Respiratory Emergency appearance

		Respiratory Emergency		Without Resp. Emergency		*P*	OR	95% CI
		n	%	n	%			
Age (years)	<40	15	21.7	32	46.3		1	1
	40–49	19	27.5	101	14.8		0.40	0.18–0.87
	50–59	53	38.7	212	38.3	0.22	0.53	0.26–1.05
	60–69	37	27.0	149	26.9		0.52	0.26–1.07
	≥70	13	9.5	59	10.7		0.47	0.19–1.10
Gender	Male	104	75.9	440	79.6	0.35	1	1
	Female	33	24.1	113	20.4		1.23	0.79–1.92
Type of Intrathoracic Malignancy	Lung Tumor	115	83.9	511	92.4	<0.001*	1	1
	Mediastinal Tumor	15	10.9	17	3.1		3.92	1.90–8.08
	Secondary Lung Tumor	7	5.1	25	4.5		1.24	0.52–2.94
Site of Tumor	Right Lung	78	67.8	293	57.5	0.04*	1	1
	Left Lung	37	32.2	217	42.5		0.64	0.41–0.98

Note: *) significant with Logistic Regression test with level of accuracy 5%

Factors that affected the respiratory appearance in intrathoracic malignancy had been analyzed using logistic regression, as can be seen in Table 3. Mediastinal tumors 3.9 times more likely related to respiratory emergency appearance with CI 1.90-8.08, while age and gender do not affect the occurrence of respiratory emergency. Factor that influences the respiratory emergency appearance in lung tumor is the location of the tumor, which is the right lung tumor 1.5 times more likely at risk of developing respiratory emergencies than the left lung tumor (Table 3).

DISCUSSION

From 690 subjects found that lung tumors cases were the most common types of intrathoracic malignancy, there are 626 lung tumor cases (90.7%), mediastinal tumors as many as 32 cases (4.6%), secondary lung tumors 32 cases (4.6%), whereas mesothelioma and chest wall tumors not found in 5 years of observation (Table 1). Male more common than women (78.8% vs 21.2%) and the highest age ranged between 50–59 years (38.4%) and 60–69 years (27%).

The results of this study are slightly similar from previous studies at H. Adam Malik General Hospital from 201 inpatient lung cancer patients were found as much as 86.1% were male with aged ≤ 60 years about 40.8%.[13] There were 137 (19.8%) intrathoracic malignancy patients presented with respiratory emergency (Table 2), these data not much different from previous studies in lung cancer patients who came to the emergency department because of respiratory complaints of 37.6%.[4]

In this study there were 45 patients (6.5%) with massive malignant pleural effusion (MPE), while the study at Persahabatan – Jakarta Hospital by Syahruddin et al. found 52.4% patients with MPE from lung cancer cases from 3 years obeservation.[14] This difference because of the sample using pleural fluid cytology that known has low sensitivity about 48.5%,[15] and also the MPE cases in this study should be a massive size pleural effusion, while other MPE sizes were excluded.

Jiminez et al. found the number of massive pleural effusions was 11.2% from all pleural effusions and 53.7% of the cases was massive pleural effusions due to malignancy.[6] Malignant pleural effusion in this study was mostly caused by lung tumors and metastatic lung tumors, this is consistent with the most common causes of MPE, which is lung cancer (36%), breast cancer (26%), lymphoma (13%), ovarian cancer (9.3%) and gastrointestinal malignancies (7.3%).[16] Sixteen patients died from 45 patients with massive MPE (35.5%), in a previous study had known that massive MPE related to poor prognosis with median survival rate of only 5 months[6]. The mortality rate due to massive MPE is quite high even though the therapy for malignancy already given (chemotherapy or radiotherapy). This is because in patients with MPE already in advance disease (stage IV) so the prognosis and survival rates are worse.

The second most common cause of respiratory emergency was Superior Vena Cava Syndrome (SVCS) from 40 patients (5.8%). This number is not much different from the study by Rowell & Gleeson (2002) who found the incidence of SVCS in lung cancer patients was 3.8%.[7] From a previous study found that malignancy was the most common cause of SVCS, which was around 94%, while mediastinal tumors 35.4% and lung tumors 22.5%.[17] In this study, as many as 14 of the 40 patients with intrathoracic malignancies hospitalized with SVCS were died (35%). Median survival rate in patients with SVCS from previous study was 5.5 months and radiotherapy emergency should be performed immediately to relief symptoms about 56–96% for 3–30 days.[18] The high mortality rate in SVCS patients is due to inappropriate management beside radiotherapy emergency, installation of endovascular stents, bypass surgery using graft from the innominate/jugular vein to the right atrium has been shown to alleviate SVCS symptoms and increase survival rates.[19]

The incidence of central airway obstruction in this study was 27 cases (3.9%), this number was lower than the previous study 13%.[8] The difference

due to the criteria of central airway obstruction (CAO) in this study was an obstruction of the main trachea and main carina whereas in previous studies included obstruction in the main bronchi. The mortality rate in patients with CAO is 37% (10/27), Similar result from prior studies whereas 44% of patients with malignancy with CAO died in one year after diagnostic.[8] Management of CAO with therapeutic bronchoscopy (such as stenting, electro cryotherapy, mechanical/thermal ablation, brachytherapy) has been shown to alleviate symptoms significantly, improve quality of life and survival rates more than twice compared with patients who were not underwent the therapy.[20]

The incidence of pneumothorax in this study was 11 patients (1.6%), this figure was slightly higher than the previous study by 0.03% to 0.05%.[11] It can be caused by other comorbidities such as COPD and previous lung infections not excluded. The mortality rate in patients with pneumothorax is 1 in 11 patients (9.09%), it shows that the management of pneumothorax cases already given such as thorax drainage (WSD) installation. Massive hemoptysis was found in 4 patient (0.6%), which was lower than the previous study (3%).[10] This condition because of patients with other comorbidities such as pulmonary tuberculosis and patients with blood clotting disorders were excluded. While in from Retno et al. Persahabatan Hospital found as many as 3.4% patient with bloody cough caused by lung cancer. In this study 50% (2/4) of patients with massive hemoptysis died, this result is consistent with studies of massive hemoptysis conservatively treated with a mortality rate of 50% to 100%.[21]

The high mortality rate of massive hemoptysis patients in this study was due to inadequate (conservative) therapy. Treatment of massive hemoptysis requires multidisciplinary collaboration where interventions such as therapeutic bronchoscopy are needed using rigid bronchoscopy and flexible bronchoscopy (with cold saline, instillation of vasoconstriction agents, forgaty balloon tamponade and stenting), cessation of bleeding using electrocautery, Nd-YAG laser and the main therapy is to embolize bronchial arteries. Study by Lee et al. (2012) in patients with massive hemoptysis who performed bronchial artery embolism reported the success rate of this treatment about 92.9%.[22]

Pulmonary thromboembolism was not found from this study due to lack of diagnostic modalities such as V/Q scan and pulmonary angiography and Well score data also incomplete. Therefore, the emergency respiratory rate may be higher considering the rate of venous thrombosis in malignant patients was 23.1%,[23] and pulmonary thromboembolism alone causes 5–10% of deaths in inpatient patients[9].

During observations, most patients died due to lung tumors and the risk of death increased in patients with respiratory emergency then patient without respiratory emergency. Increased of mortality in patients with respiratory emergency compared to those without emergencies makes it important to know what factors related to the respiratory emergency occurrence in intrathoracic malignancy. From Table 3 can be seen that the type of intrathoracic malignancy significantly affects the incidence of respiratory emergency (P<0.001). Also, can be seen that mediastinal tumors are 3.9 times more likely to cause respiratory emergency compare to lung tumors. This is due to a tumor in the mediastinal cavity (an imaginary cavity between the left and right lungs). This cavity is anatomically filled with important organs such as the heart, arteries, veins, trachea, thymus gland, nerves, connective tissue, lymph nodes and channels. This cavity is narrow and stiff, so that if there is a tumor in this area it will suppress the surrounding organs and cause life-threatening emergencies, such as suppression of the trachea (CAO), suppression of the superior vena cava (SVCS), suppression of lymph glands (pleural effusion).

Factors that influence the respiratory emergency appearance in lung tumors was the location of the tumor, where the right lung tumor is 1.5 times more likely to cause a respiratory emergency than the left lung tumor. From study observations, it was found that respiratory

emergencies that often appear in the right lung tumor, such as SVCS, this is because the location of the tumor in the right lung is anatomically close to the superior vena cava.

CONCLUSION

From 137 patients with respiratory emergency found that lung tumors were the most common causes (83.9%). The most common respiratory emergency was massive MPE (6.5%) and massive hemoptysis is the rarest cases (0.6%). Mortality rate was higher in patients with respiratory emergency. Factors related to the respiratory emergency occurrence in intrathoracic malignancy patients were the type of malignancy and the site of the tumor.

Mortality rate was higher in patients with respiratory emergency and patient with intrathoracic malignancy need immediate treatment collaboration between multidisciplinary to relief symptom and improve quality of life and survival rates.

REFERENCES

1. Perhimpunan Dokter Paru Indonesia. Kanker Paru Pedoman diagnosis dan penatalaksanaan di Indonesia. Jakarta; 2016. 1 p.
2. Cervantes A, Chirivella I. Oncological emergencies. Ann Oncol Off J Eur Soc Med Oncol. 2004;15 Suppl 4:iv299-306.
3. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ CK (eds). SEER Cancer Statistics Review 1975-2013 National Cancer Institute SEER Cancer Statistics Review 1975-2013 National Cancer Institute. National Cancer Institute. 2016.
4. Minami S, Yamamoto S, Ogata Y, Takeuchi Y, Hamaguchi M, Koba T, et al. Emergency department visits after hours by lung cancer patients in Japan. Support Care Cancer. 2013;21(9):2443–51.
5. Djojodibroto D. Respirologi (Respiratory Medicine). Jakarta: EGC; 2009. 269 p.
6. Jiménez D, Díaz G, Gil D, Cicero A, Pérez-Rodríguez E, Sueiro A, et al. Etiology and prognostic significance of massive pleural effusions. Respir Med. 2005;99(9):1183–7.
7. Kinnard E. Superior vena cava syndrome in the cancer patient: a case study. J Adv Pract Oncol. 2012;3(6):385–7.
8. Daneshvar C, Falconer WE, Ahmed M, Sibly A, Hindle M, Nicholson TW, et al. Prevalence and outcome of central airway obstruction in patients with lung cancer. BMJ open Respir Res. 2019;6(1):e000429.
9. Perhimpunan Onkologi Indonesia. Kedaruratan onkologi II : kedaruratan neurorespiratori pada kanker. Ranuhardy D, editor. Jakarta: Badan Penerbit FKUI; 2010. 41–53 p.
10. Yeung S-CJ, Escalante CP. Respiratory Oncologic Emergencies. 6th ed. Donald W kufe M, Raphael E Pollock, MD P, Ralph R Weichselbaum M, Robert C Bast, Jr M, Ted S Gansler, MD M, James F Holland, MD S (hc), et al., editors. BC Decker; 2003.
11. Vencevicius V, Cicenas S. Spontaneous pneumothorax as a first sign of pulmonary carcinoma. World J Surg Oncol. 2009;7:57.
12. Kosasih A, Susanto AD, Pakki TR, Martini T. Diagnosis dan Tatalaksana Kegawatdaruratan Paru dalam Praktek Sehari-hari. Jakarta: Sagung Seto; 2008. 1–100 p.
13. Saragih HM. Profil Penderita Kanker Paru yang Dirawat di Rindu A3 (RA3) RSUP Haji Adam Malik Medan Tahun 2007-2010. Universitas Sumatera Utara. 2012.
14. Syahruddin E, Hudoyo A, Arief N. Efusi pleura ganas pada kanker paru. J Respir Indo. 2009;29(4):1–9.
15. Bielsa S, Panadés MJ, Egido R, Rue M, Salud A, Matías-Guiu X, et al. [Accuracy of pleural fluid cytology in malignant effusions]. An Med Interna. 2008;25(4):173–7.
16. Zamboni MM, da Silva CT, Baretta R, Cunha ET, Cardoso GP. Important prognostic factors for survival in patients with malignant pleural

effusion. BMC Pulm Med. 2015;15(1):29.

17. Pech-Alonso B, Fermín-Hernández C, Saavedra-de Rosas SI, Cicero-Sabido RJ. Superior vena cava syndrome: Clinical considerations. Rev Médica del Hosp Gen México. 2018;81(2):59–65.
18. Straka C, Ying J, Kong F-M, Willey CD, Kaminski J, Kim DWN. Review of evolving etiologies, implications and treatment strategies for the superior vena cava syndrome. Springerplus. 2016;5(1):229.
19. Doty JR, Flores JH, Doty DB. Superior vena cava obstruction: bypass using spiral vein graft. Ann Thorac Surg. 1999;67(4):1111–6.
20. Stratakos G, Gerovasili V, Dimitropoulos C, Giozos I, Filippidis FT, Gennimata S, et al. Survival and Quality of Life Benefit after Endoscopic Management of Malignant Central Airway Obstruction. J Cancer. 2016;7(7):794–802.
21. Mehta AS, Ahmed O, Jilani D, Zangan S, Lorenz J, Funaki B, et al. Bronchial artery embolization for malignant hemoptysis: a single institutional experience. J Thorac Dis. 2015;7(8):1406–13.
22. Lee BR, Yu JY, Ban HJ, Oh IJ, Kim KS, Kwon YS, et al. Analysis of patients with hemoptysis in a tertiary referral hospital. Tuberc Respir Dis (Seoul). 2012;73(2):107–14.
23. Majidiah F, Sjahruddin E, Andarini SL. Trombosis Vena Dalam pada Pasien Kanker Paru Berdasar Kriteria Wells Deep Vein Trombosis among Lung Cancer Patients Using Wells Score. J Respirologi Indones. 2013;34(1):1–10.

Concordance of TST and QFT-Plus, Sensitivity and Specificity of TST and QFT-Plus in Detection of LTBI in MDR TB Contact

Rullyano Hardian, Reviono, Harsini, Yusup Subagio Sutanto

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

Abstract

Background: *Tuberculosis (TB) is an infectious disease and the main cause of world health problems. Not all individuals infected with Mycobacterium tuberculosis (Mtb) develop active TB. Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation of the Mtb antigen with no evidence of clinically manifest active TB. Closed contact and household contact with MDR TB patients increases the risk of MDR TB transmission. There is no gold-standard test for LTBI. Tuberculin Skin Test (TST) and Quantiferon Gold Plus (QFT-Plus) examinations are used for LTBI diagnosis.*

Methods: *A cross-sectional diagnostic test of 32 MDR TB contacts, consisting of 16 household contacts and 16 close contacts, was conducted in April 2020 at Dr. Moewardi Surakarta Hospital.*

Results: *Positive TST results among MDR TB contacts were 18.8%, while QFT-Plus positive was 25%. The concordance level of TST and QFT-Plus was nearly perfect (κ=0.818, p<0.001). The sensitivity and specificity of QFT-Plus with household contacts as the gold standard were 37.5% and 87.5%, respectively. The sensitivity and specificity of TST with household contacts as the gold standard were 25% and 87.5%, respectively.*

Conclusion: *The concordance level of TST and QFT-Plus in the detection of LTBI in MDR TB contacts was very good. The TST can be used in place of QFT-Plus although QFT-Plus has better sensitivity. Both tests are useful for confirming TB infections. Both of these tests are not diagnostic, however they can be used to screen for LTBI in MDR TB contacts.* ***(J Respirol Indones 2022; 42(1): 9–17)***

Keywords: *TST, QFT-Plus, Contact, MDR TB*

Tingkat Kesesuaian TST dengan QFT-Plus Serta Sensitivitas dan Spesifisitas TST Dengan QFT-Plus dalam Mendeteksi LTBI pada Kontak TB MDR

Abstrak

Latar belakang: *Tuberkulosis (TB) merupakan penyakit infeksi penyebab utama masalah kesehatan dunia. Tidak semua individu terinfeksi Mycobacterium tuberculosis (Mtb) akan berkembang menjadi TB aktif. Infeksi tuberkulosis laten (LTBI) adalah keadaan respon imun persisten terhadap stimulasi antigen Mtb dengan tanpa adanya bukti dan tanda klinis TB aktif. Kontak serumah dan erat dengan pasien TB MDR meningkatkan risiko penularan TB MDR. Baku emas diagnosis LTBI saat ini tidak ada. Pemeriksaan Tuberculin Skin Test (TST) dan Quantiferon Gold Plus (QFT-Plus) digunakan untuk diagnosis LTBI.*

Metode:*Uji diagnostik cross sectional terhadap 32 kontak TB MDR, terdiri 16 kontak serumah, dan 16 merupakan kontak erat dilakukan pada April 2020 di RSUD dr. Moewardi Surakarta.*

Hasil: *Tingkat kesesuaian TST dan QFT-Plus adalah sangat baik (κ = 0,818, p < 0,001). Sensitivitas dan spesifisitas QFT-Plus dengan kontak serumah sebagai baku emas sebesar 37,5% dan 87,5%. Sensitivitas dan spesifisitas TST dengan kontak serumah sebagai baku emas sebesar 25% dan 87,5%.*

Kesimpulan: *TST positif pada kontak TB MDR didapatkan sebesar 18,8% sedangkan QFT-Plus positif sebesar 25%. Tingkat kesesuaian TST dengan QFT-Plus dalam deteksi LTBI pada kontak TB MDR adalah sangat baik. Pemeriksaan TST dapat menggantikan pemeriksaan QFT-Plus. QFT-Plus memiliki sensitivitas yang lebih baik. Kedua pemeriksaan baik untuk memastikan infeksi oleh TB. Kedua pemeriksaan kurang baik untuk diagnosis, namun masih dapat digunakan untuk skrining pada kontak TB MDR.* ***(J Respirol Indones 2022; 42(1): 9-17)***

Kata kunci: *TST, QFT-Plus, Kontak, TB MDR*

Correspondence: Rullyano Hardian
Email: rullyanoh@gmail.com

INTRODUCTION

Tuberculosis (TB) is an infectious disease that continues to be the leading cause of global health issues. Mycobacterium tuberculosis (Mtb) has been influencing and developing human existence for thousands of years. The success has persisted for thousands of years because it may remain latent, asymptomatic, and then reactivate as active TB. Not all individuals infected with Mtb will develop active TB. Tuberculosis is one of the top ten causes of mortality globally, as well as the primary cause of death from an infectious agent.[1–3]

Not all individuals infected with Mtb will develop active TB. Fifty to 70% of individuals exposed to MTb can overcome their TB infection through innate or adaptive immune mechanisms. The remaining 30–50% will be active TB or LTBI. Latent tuberculosis infection (LTBI) is a state of persistent immune response to Mycobacterium tuberculosis antigen stimulation without any evidence or clinical signs of active TB. Individuals infected with MTb have a high risk of developing active TB. Every year, LTBI progression to active TB contributes to an increase in the incidence of active TB. Active tuberculosis occurred in 7.7% of LTBI patients after one year of infection and 14.2% at the end of 2020. Prevention of active TB originating from LTBI reactivation is an important component of the WHO End TB Strategy program. End TB program targets cannot be achieved without involving LTBI management.[3–5]

The large global burden of LTBI is a potential source of TB transmission in the future. The global burden of LTBI in 2016 was around 1.7 billion people, or a quarter of the world's population. The Southeast Asia region bears more than 40% of the global TB incident burden and nearly 35% of the world's LTBI burden. The burden on the Southeast Asian region is disproportionate, considering that only about 26% of the global population lives in this region. The current response to the TB situation in the Southeast Asia region needs to be accelerated as soon as possible to achieve significant progress towards achieving the *End TB Strategy's* targets.[3–5]

Antimicrobial resistance is an increasingly serious threat to public health globally. Multidrug-resistant (MDR) Mtb strains, resistant to both first-line TB drugs (rifampin and isoniazid), are responsible for about a quarter of all deaths caused by antimicrobial-resistant infections. WHO data shows around 558,000 cases of MDR TB or Rifampicin resistant (RR) worldwide. Household and close contact with MDR TB patients increases the risk of MDR TB transmission. The latent TB patients who come into contact with MDR TB patients is a potential burden for increasing MDR TB incidence. Close contact with TB and MDR-TB patients, especially children and people living in low-income countries, is highly likely to develop MDR-TB. The risk of spreading the disease from index cases to contacts will increase if there is a delay in diagnosis and treatment. Research by Fox et al. (2017) in Vietnam found the prevalence of positive TST results in contacts with MDR TB patients was 40.8%. Husein et al. (2019) found that the prevalence of LTBI in the contact group with with TB in Duhok city, Iraq, was high at 41.3% (62/150). This burden must be addressed to prevent a global epidemic of MDR TB. Prevention of the increased incidence of MDR TB from latent TB caused by MDR strains is very important for the success of TB control programs.[6–10]

The diagnosis of LTBI can be a challenge because there is no gold-standard check. The number of bacteria in LTBI individuals is unknown, but it is believed to be so small that it is impossible to directly examine Mtb bacteria, so an immunological examination is carried out instead. The diagnosis of LTBI is made through the *tuberculin skin test* (TST) or the *interferon-gamma release assay* (IGRA). This research used QFT-Plus with the consideration of having better specificity and sensitivity. Because the QFT-Plus test is expensive and difficult to get in laboratory facilities, the TST is better-suited for situations in Indonesia with a high prevalence of tuberculosis. The TST is not only inexpensive, but also easy to do and obtain. The background of this study stems

from the disparity in data availability, diagnostic methods appropriate for Indonesian settings, and LTBI treatment of MDR TB contacts. This study aims to provide information regarding early detection of LTBI in MDR TB contacts.[5,11]

Furthermore, this study was specifically done to compare the applicability of TST and QFT-Plus examination results in identifying LTBI in MDR TB contacts, as well as finding the difference in sensitivity and specificity of both tests in detecting LTBI in MDR TB contacts. Furthermore, this study was specifically done to compare the applicability of TST and QFT-Plus examination results in identifying LTBI in MDR TB contacts, as well as finding the difference in sensitivity and specificity of both tests in detecting LTBI in MDR TB contacts. By providing fundamental data of prevalence statistics and diagnostic procedures through this study, our research team hope this could be useful for future reference to establish LTBI detection and prevention strategies.

METHODS

This study is a cross-sectional diagnostic test study in which the independent and dependent variables were measured simultaneously for the TST and QFT-Plus examinations. The research was conducted at Dr. Moewardi Hospital, Surakarta Sragen, in April 2020 to meet the number of samples. The sample in this study was MDR TB contacts who were not sick with TB or had had TB disease. The inclusion criteria in this study were people >18 years of age who were willing to participate in the study. The exclusion criteria for this study were a person with clinical signs or symptoms of TB, or a history of TB, a history of taking anti-tuberculosis drugs (OAT), a history of severe allergic reactions or hypersensitivity to a previous TST examination (necrosis, ulceration, anaphylactic shock), or someone with comorbid disease and immunosuppressive disease (DM, clinical HIV, renal failure, and the use of corticosteroids). Subjects who do not return within 48–72 hours for a TST evaluation or withdraw are considered discontinuous.

A person in contact with MDR TB patients who agreed and met the inclusion criteria was asked to sign an informed consent. The sample consisted of 32 MDR TB contacts, divided into 16 household contacts and 16 close contacts. Subjects who met the inclusion criteria were then given education and recorded data, including identity, history taking, physical examination, laboratory examination, TST examination, and QFT-Plus. Subjects are required to be re-examined within 48-72 hours for TST readings.

Data analysis is presented in the distribution of frequency and percentage. Kappa Cohen test was used to calculate the degree of concordance between TST and QFT-Plus. The correlation analysis used in this research is contingency coefficient analysis. Data on all variables were analyzed using SPSS 22 for windows. The non-existent gold standard for establishing the diagnosis of LTBI is a problem in determining the diagnostic accuracy of TST and IGRA. Comparing patients at high risk of exposure to active TB or patients with LTBI at high risk of acquiring active TB is an alternate method of determining sensitivity that cannot be tested directly.

RESULT

This study was conducted on 32 MDR TB contact respondents with the characteristics of gender, age, type of contact, education level, nutritional status (BMI), and BCG scar. Respondents in this study had a proportion of middle-aged (41-60 years) greater than other age groups, namely as much as 50%. The results of the QFT-Plus and TST that were positive were mostly found in respondents in the middle-aged group, namely 12%, with a total of 4 respondents, and 5.6% of respondents with positive QFT-Plus.

The number of female respondents was 17 (53.1%), while the number of male respondents was 15 (46.9%). The results of the positive QFT-Plus and TST examinations were mostly found in female respondents (18.8%), with a total of six respondents

and seven (21.9%) respondents with positive QFT-Plus.

Based on the type of contact (household contacts with close contacts), the number of respondents is the same, namely 16 people each, or 50% of the respondents. The results of positive TST and QFT-Plus examinations were more common in the household contact variable group than in close contacts, which was 12.5%, with a total of four respondents having positive TST results and six respondents (18.8%) having positive QFT-Plus results. This value is higher than the positive immunological examination results in close contact, namely two (6.3%) positive TST respondents and two (6.3%) positive QFT-Plus.

Most of the research respondents have a very high educational background or have a college education, as many as 15 (46.9%) respondents. Most of the research respondents were respondents with normal nutritional status, as many as 16 (50%), while for those with poor nutritional status, the proportion was two (6.2%). Most of the research respondents were found to have BCG scars, as much as 75%.

Cross tabulation of positive QFT-Plus examination results with positive TST results in 6 (18.8%) respondents and positive QFT-Plus results with negative TST results in as many as 2 (6.3%) respondents. Negative QFT-Plus examination and positive-negative TST were not obtained in this study, so 0.0%. As many as 24 (75%) respondents obtained a negative QFT-Plus examination and a negative TST.

The degree of conformity (Kappa) of the TST examination with QFT-Plus in this study was 0.818 with a p-value of < 0.001 statistically significant. The data above shows that the level of conformity of the two examinations is very good (kappa value: > 0.8). The level of conformity of the TST examination with QFT-Plus in detecting LTBI in MDR TB contacts can be seen in Table 2.

Table 1. Characteristics of Research Subject

Characteristics	Total Subject n (%)	TST (+) n (%)	QFT-Plus (+) n (%)
Age			
Early adulthood (18–40) years)	14 (43,8%)	2 (6,3%)	3 (9,4%)
middle-aged (41–60)	16 (50%)	4 (12,5%)	5 (15,6%)
Older adults (>61)	2 (6,2%)	0 (0,0%)	0 (0,0%)
Gender			
Female	17 (53,1%)	6 (18,8%)	7 (21,9%)
Male	15 (46,9%)	0 (0,0%)	1 (3,1%)
Contact type			
Household Contact	16 (50%)	4 (12,5%)	6 (18,8%)
Close Contact	16 (50%)	2 (6,3%)	2 (6,3%)
Level of Education			
Low (Elementary)	6 (18%)	0 (0,0%)	0 (0,0%)
Medium (Junior High School or equivalent)	1 (3,1%)	1 (3,1%)	1 (3,1%)
High (Senior High School)	10 (31,3%)	2 (6,3%)	4 (12,5%)
Very high (College)	15 (43,8%)	3 (9,4%)	3 (9,4%)
Nutritional Status (BMI)			
Less BMI	2 (6,2%)	0 (0,0%)	0 (0,0%)
Normal BMI	16 (50%)	4 (12,5%)	5 (15,6%)
Excess BMI	14 (43,8%)	2 (6,3%)	3 (9,4%)
Scar BCG			
Exist	24 (75%)	5 (15,6%)	7 (21,9%)
None	8 (25%)	1 (3,1%)	1 (3,1%)

Table 2. Conformity of TST and QFT-Plus in detecting LTBI in MDR TB contacts

Group		TST		Total	Kappa (κ)	*P*
		Positive	Negative			
QFT-Plus	Positive	6	2	8	0,818	<0,01
	Negative	0	24	24		
Total		6	26	32		

Note: κ = kappa; *P*<0,001 means significant

Table 3. The results of the sensitivity test, the specificity of the QFT-Plus examination for MDR-TB household contacts

		Household Contact Positive	Household Contact Negative	Total
QFT-Plus	Positive	6	2	8
	Negative	10	14	24
	Total	16	16	32
Sensitivity	=	37,5%		
Specificity	=	87,5%		
Positive predictive value	=	75%		
Negative predictive value	=	58,3%		
Positive probability ratio	=	3		
Negative probability ratio	=	0,7		

The results of the QFT-Plus sensitivity test for MDR TB household contacts in this study were 37.5%. The sensitivity value obtained means detecting 37.5% of respondents with positive household contacts with QFT-Plus. The specificity value of the QFT-Plus examination on MDR TB household contacts is 87.5%, which means that the possibility of negative household contacts that can be excluded for respondents who have a positive QFT-Plus is 87.5%. The positive predictive value of QFT-Plus in this study was 75%, and the negative predictive value in this study was 58.3%. This study's QFT-Plus positive chance ratio was 3, with a negative probability ratio of 0.7. The sensitivity and specificity of QFT-Plus to MDR TB household contacts can be seen in Table 3.

Table 4. Results of sensitivity test, specificity of TST examination for MDR TB household contacts.

		Household Contact Positive	Household Contact Negative	Total
TST	Positive	4	2	6
	Negative	12	14	26
	Total	16	16	32
Sensitivity	=	25%		
Specificity	=	87,5%		
Positive predictive value	=	66,6%		
Negative predictive value	=	53,8%		
Positive probability ratio	=	2		
Negative probability ratio	=	0,8		

The results of the TST sensitivity test for MDR TB household contact respondents in this study were found to be 25%. The sensitivity value obtained means that TST can detect 25% of respondents with positive household contacts. The specificity value of the TST on MDR TB household contacts is 87.5%, which means that the possibility of negative household contacts that can be excluded in respondents who have a positive TST is 87.5%.

Table 5. Correlation of research subject characteristics to QFT-Plus and TST

Characteristics	QFT-Plus (+) n (%)	QFT-Plus (-) n (%)	Total n (%)	*P*	TST (+) n (%)	TST (-) n (%)	Total N (%)	*P*
Gender				0.025				0.011
Female	7 (21.9)	10 (31.1)	17 (53.1)		6 (18,8)	11(34,4)	17 (53,1)	
Male	1 (3.1)	14(43.8)	15 (46.9)		0 (0)	15 (46,9)	15 (46,9)	
Age				0.578				0.590
Early adulthood (18–40 years)	3 (9.4)	11(34.4)	14 (43.8)		2 (6,3)	12 (37,5)	12 (43,8)	
middle-aged (41–60 years old)	5 (15.6)	11 (34.4)	16 (50)		4 (12,5)	12 (37,5)	16 (50)	
Older adults (>61 years)	0 (0)	2 (6.3)	2 (6.2)		0 (0)	2 (6,3)	2 (6,3)	
Contact Type				0.102				0.365
Household Contact	6(18.8)	10(31.3)	16 (50)		4(12,5)	12(37,5)	16 (50)	
Close Contact	2(6.3)	14(43.8)	16 (50)		2(6,3)	14(43,8)	16 (50)	
Level of education				0.094				0.125
Low (Elementary)	0 (0)	6 (18.8)	6 (18.8)		0 (0,0)	6 (18,8)	6(18,8)	
Medium (Junior High School)	1 (3.1)	0 (0)	1 (3.1)		1 (3,1)	0 (0)	1 (3,1)	
High (Senior High School)	4 (12.5)	6 (18.8)	10 (31.3)		2 (6,3)	8 (25)	10 (31,3)	
Very High (College)	3 (9.4)	12 (37.4)	15 (43.8)		3 (9,4)	12 (37,5)	15 (46,9)	
Nutritional Status (BMI)				0.578				0.590
Less BMI	0 (0)	2 (6.2)	2 (6.2)		0 (0)	2 (6,3)	2 (6,3)	
Normal BMI	5 (15.6)	11 (34.4)	16 (50)		4 (12,5)	12 (37,5)	16 (50)	
Excess BMI	3 (9.4)	11 (34.4)	14 (43.8)		2 (6,3)	12 (37,5)	14 (43,8)	
Scar BCG				0.346				0.601
Exist	7 (21.9)	17 (53.1)	24 (75)		5 (15,6)	19 (59,4)	24 (75)	
None	1 (3.1)	7 (21.9)	8 (25)		1 (3,1)	7 (21,9)	8 (25)	

The positive predictive value of TST in this study was 66.6%, and the negative predictive value in this study was 53.8%. The TST positive probability ratio is 2, and the negative probability ratio is 0.8. The sensitivity test and the specificity of TST for MDR TB household contacts can be seen in Table 4.

Male respondents tend to have a negative QFT-Plus examination (43.8%), while female respondents with a negative QFT-Plus examination are 31.3%. There was a significant correlation with gender and with QFT-Plus (r=0.370 and *P*=0.025) or TST (r=0.411 and *P*=0.011). This research did not find a statistically significant correlation between age, type of contact, education level, nutritional status, and BCG scar with the TST or QFT-Plus examination. In Table 5, the correlation between the characteristics of the research subjects (gender, age, type of contact, education level, nutritional status, and BCG scar) on the QFT-Plus and TST examinations can be seen.

DISCUSSION

This study obtained positive TST examinations from six (18.8%) subjects, while the QFT-Plus examination obtained more positive results, namely eight (25%) respondents. The number of positive TSTs on MDR TB contacts obtained in this study was less when compared to the study conducted by Nguyen et al. (2015) in Ho Chi Minh City, Vietnam, where subjects received positive TST in 39% of MDR TB contacts.[12]

At the positive QFT-Plus examination, with a positive TST, there were six subjects, or 18.8%, and at the positive QFT-Plus examination, with a negative TST, there were two subjects, or 6.3%. Two respondents with positive QFT-Plus and negative TST results have the characteristics that they are household contacts, are part of the young and middle-aged age groups, and have normal and excess nutritional status.

Negative QFT-Plus examination with negative TST obtained by 24 (75%) respondents. The number of negative TST in MDR TB contacts obtained in this study was greater than the study results by Fox et al. (2017) on 147 contacts of MDR TB patients in Vietnam, where negative TST results were obtained by 59.18% subjects.[6] The results of the TST and QFT-Plus examinations were negative 75% in this study, which could bedue to several things. The first is that there are 75% of contacts who are not infected by Mtb. This is based on the theory that about 50–70% of individuals exposed to Mtb can overcome the infection (PDPI, 2016).[5] Second, negative TST results in this study could be false negatives. False-negative TST results can occur because the infection occurred in less than 8-10 weeks. On the other hand, false-negative TST results can also occur due to long exposure and infection. Third, the results of the LTBI examination in many studies were negative. This could also be due to the fact that this study did not include vulnerable populations such as infants and children, especially those aged <5 years. In their study, Golla et al. (2017) found a prevalence of 44.7% of positive TST in children aged <5 years who were in contact with MDR TB patients.[13]

The level of conformity between TST and QFT-Plus as a diagnostic tool the LTBI degree of conformity (Kappa) TST examination with QFT-Plus was 0.818, with *P*<0.001 statistically significant. The excellent concordance rate means that the TST examination can detect LTBI in MDR TB contacts. Researchers have not received a study of the suitability of QFT-Plus with TST against MDR TB contacts (household and close contacts). The study of the QFT-Plus conformity test with TST was conducted by Venkatappa et al. (2019) in the United States, October 2016 to May 2017, on high-risk populations including close contacts, immigrants, homeless people, inmates, and those with a history of travel to countries with high TB rates. This study found that the level of conformity between QFT-Plus and TST was sufficient (κ=0.46).[14] Abdulkareem's research (2019) in Kurdistan, Iraq, tested the suitability of QST Plus - TST, conducted in May-October 2018 on 521 household contacts of active TB patients. This study found that the level of

conformity of the QFT-Plus examination with TST was good (κ=0.679).[15]

The TST examination has several disadvantages compared to the QFT-Plus, resulting in false positives and negatives.[4] The excellent match rate between TST and QFT-Plus means that the TST examination can be used as a diagnostic tool to detect LTBI equivalent to QFT-Plus. The TST examination can replace the QFT-Plus examination for LTBI detection in MDR TB contacts.

The specificity value of QFT-Plus and TST is 87.5%, which means that this test is good for confirming LTBI in MDR TB contacts because of its high specificity. The low sensitivity value (QFT-Plus 37.5% vs. TST 25%) means that this test is less sensitive for diagnosing LTBI in MDR TB contacts, so additional tests are needed for diagnosis. The sensitivity and specificity of TST in LTBI for high-risk groups have been reported in several studies. A previous study by Sinaga (2017), which assessed the sensitivity of LTBI to CD4+ cell count 200 mm^3, found that the TST sensitivity was 28.6%, and the specificity was 81.7%. The Triyoga study (2018) assessed the specificity and sensitivity of TST in medical personnel, finding a higher TST performance with a sensitivity of 33.33% and a specificity of 93.30%. This tool can still be used for screening to detect LTBI in MDR TB contacts. Despite getting low sensitivity on both examinations, this study shows that the sensitivity value of QFT-Plus is better than TST.[11,16]

There is a significant correlation between gender and TST and QFT-Plus with a moderate correlation value because, in this study, the index cases of MDR TB were mostly male. Subjects with positive TST and QFT-Plus from the household contact group were partners (wives) of the index cases.

This study did not find a statistically significant correlation between age, education level, nutritional status, and BCG scar with TST or QFT-Plus examination. These results follow the research of Fox et al. (2017) on 180 respondents who were in contact with drug-sensitive TB patients and 147 respondents who had contacts with MDR TB patients in Vietnam.[6] There was no statistically significant relationship between age, gender, occupation, education level, and previous history of BCG immunization with positive TST.[5] Based on age, the most positive TST was in the middle adult age group, which was 12.5% according to the research of Eom et al. (2017) in Busan, South Korea, for respondents aged >18 years who were household contacts of TB patients who received the highest number of positive TST in the middle-aged group, namely 36 out of 188 (19%) respondents.[17]

Poor nutritional status causes a person's susceptibility to infection, but a meta-analysis study by Saag et al. (2018) found that poor nutritional status did not significantly correlate with LTBI. A study by Chadra (2009) on children with Z-scores BMI also did not find an increase in the prevalence of positive TST in severe malnutrition compared to moderate degrees. This is in accordance with the WHO recommendation not to carry out systematic examinations for LTBI in people with poor nutritional status.[18]

The history of BCG vaccination had no effect on the QFT-Plus assessment. The TST examination may be influenced by a booster effect caused by a history of past BCG vaccine administration, although the World Health Organization maintains that vaccination history has a limited influence on the specificity of the tuberculin test since BCG cross-reactivity declines over time.[3]

The limitation of this study is that there is no gold-standard diagnostic test for LTBI. An alternative way of assessing sensitivity and specificity that cannot be assessed directly by comparing the gold standard is to compare subjects at high risk of exposure to active TB patients or subjects with LTBI who are at risk of developing active TB. Selection of household contacts as a substitute for the gold standard because they have a high risk of exposure to Mtb.[19,20]

CONCLUSION

Because the TST and QFT-Plus have a high degree of concordance, the two tests can be utilized

interchangeably. QFT-Plus can be replaced by examination and vice versa. TST can be used instead of QFT-Plus to identify LTBI in MDR TB contacts. QFT-Plus has a sensitivity of 37.5% while TST has a sensitivity of 25%. In this investigation of MDR TB contacts, the QFT-Plus and TST exams demonstrated a high specificity of 87.5%.

The lack of a gold-standard necessitates consensus on a certain method to be utilized as the gold-standard, therefore it is recommended that cohort studies be employed for future study. Because the QFT-Plus test has higher sensitivity and specificity than TST, it is suggested for detecting LTBI in MDR TB contacts. Because the QFT-Plus test has higher sensitivity and specificity than TST, it is suggested for detecting LTBI in MDR TB contacts.

REFERENCES

1. World Health Organization. Global tuberculosis report 2019. Geneva; 2019.
2. Burhan E, Ramdhani RR, Zaini J. Proporsi tuberkulosis laten pada pasien kanker paru di Rumah Sakit Umum Pusat Persahabatan Jakarta. J Respirologi Indones. 2019;39(4):256–65.
3. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management [Internet]. Geneva: World Health Organization; 2018. Available from: https://apps.who.int/iris/handle/10665/260233
4. World Health Organization. South-East Asia Regional Action Plan on Programmatic Management of Latent Tuberculosis Infection [Internet]. New Delhi: World Health Organization. Regional Office for South-East Asia; 2019. Available from: https://apps.who.int/iris/handle/10665/326897
5. Perhimpunan Dokter Paru Indonesia. Pedoman tatalaksana infeksi TB laten. Indonesia; 2016.
6. Fox GJ, Anh NT, Nhung N V, Loi NT, Hoa NB, Ngoc Anh LT, et al. Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. Int J Tuberc lung Dis. 2017;21(3):297–302.
7. Lokhande RM, B F. Study of tuberculosis burden in adult house hold close contacts of sputum smear positive index cases of MDR tuberculosis. Glob J Res Anal. 2019;8(2):36–7.
8. Knight GM, McQuaid CF, Dodd PJ, Houben RMGJ. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. Lancet Infect Dis. 2019;19(8):903–12.
9. Hussein N, Balatay A, Almizori L, Saifullah H. A Study of The Prevalence of Latent Tuberculosis in Household Contacts of Patients with Active Tuberculosis in Kurdistan Region of Iraq: A Brief Report. Int J Infect Press. 2019;6(2):10–2.
10. Gaskell KM, Allen R, Moore DAJ. Exposed! Management of MDR-TB household contacts in an evidence light era. Int J Infect Dis. 2019;80S:S13–6.
11. Sinaga F, Reviono, Harsini. Validitas dan reliabilitas pemeriksaan TST dan T-SPOT dalam mendeteksi infeksi TB laten pada penderita infeksi HIV. J Ilmu Kedokt Dan Kesehat. 2017;4(4):248–59.
12. Anh NT, N N V, Loi NT, Nguyen K, A LN, Buu TN, et al. The prevalence of latent TB infection among household contacts of multi-drug resistant and new tuberculosis patients in Ho Chi Minh city, Vietnam. In: The 5th Conference of the Union Asia-Pacific Region. Sydney; 2015.
13. Golla V, Snow K, Mandalakas AM, Schaaf HS, Du Preez K, Hesseling AC, et al. The impact of drug resistance on the risk of tuberculosis infection and disease in child household contacts: a cross sectional study. BMC Infect Dis. 2017;17(1):593.
14. Venkatappa TK, Punnoose R, Katz DJ, Higgins MP, Banaei N, Graviss EA, et al. Comparing QuantiFERON-TB Gold Plus with Other Tests To Diagnose Mycobacterium tuberculosis Infection. J Clin Microbiol. 2019;57(11):e00985-19.

15. Abdulkareem FN, Merza MA, Salih AM. First insight into latent tuberculosis infection among household contacts of tuberculosis patients in Duhok, Iraqi Kurdistan: using tuberculin skin test and QuantiFERON-TB Gold Plus test. Int J Infect Dis. 2020;96:97–104.
16. Triyoga PA. Tingkat kesesuaian pemeriksaan tuberculin skin test (TST) dengan T-SPOT.TB, dan sensitivitas serta spesifitas TST DAN T-SPOT.TB dalam mendeteksi infeksi TB laten pada tenaga kesehatan. Universitas Sebelas Maret; 2019.
17. Eom JS, Kim I, Kim W-Y, Jo E-J, Mok J, Kim M-H, et al. Household tuberculosis contact investigation in a tuberculosis-prevalent country: Are the tuberculin skin test and interferon-gamma release assay enough in elderly contacts? Medicine (Baltimore). 2018;97(3):e9681.
18. Saag LA, LaValley MP, Hochberg NS, Cegielski JP, Pleskunas JA, Linas BP, et al. Low body mass index and latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2018;22(4):358–65.
19. Girardi E, Angeletti C, Puro V, Sorrentino R, Magnavita N, Vincenti D, et al. Estimating diagnostic accuracy of tests for latent tuberculosis infection without a gold standard among healthcare workers. Euro Surveill. 2009;14(43):19373.
20. Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM. Evaluation of diagnostic tests when there is no gold standard. A review of methods. Health Technol Assess. 2007;11(50):iii, ix–51.

Analysis of Comorbidity and Its Association with Disease Severity and Mortality Rate in Hospitalized COVID-19 Patients

Anthony Christanto, Aditya Sri Listyoko, Ngakan Putu Parsama Putra

Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Brawijaya, RSUD Saiful Anwar, Malang

Abstract

Background: *Comorbidity is a major factor in determining the outcome of COVID-19. However, existing studies regarding comorbidities and the disease severity and mortality of COVID-19 are mostly based on studies in the whole community, and not on those admitted to hospitals. This study aims to determine the demographic profile of comorbidities among COVID-19 patients hospitalized in tertiary care referral hospitals and its association with disease severity and mortality.*

Methods: *We analyzed the data from 60 laboratory-confirmed patients in our hospital in Malang City, East Java, Indonesia from March 12th, 2020 to June 5th, 2020. We describe the demographic profile of the patients and perform statistical analysis to determine its relationship to disease severity and mortality.*

Results: *The majority of the study samples (66.7%) were categorized as having a severe disease. Thirty-seven samples (61.7%) had at least one comorbidity. The mortality rate among the study population is 30.0%, and 37.8% among those with comorbidities. The most prevalent comorbidity was hypertension (40.0%), followed by heart failure (35.0%) and diabetes (25.0%). There is a statistically significant relationship between the presence of comorbidities and disease severity and between disease severity and mortality ($p<0.05$). Diabetes was the only comorbidity with a significant relationship towards mortality in our study ($p<0.05$, OR 4.0 95% CI 1.16-13.74).*

Conclusion: *Comorbidities are associated with worse disease severity and death in hospitalized COVID-19 patients.* ***(J Respirol Indones 2022; 42(1): 18–25)***

Keywords: *Comorbidities; COVID-19; Disease Severity, Mortality Rate*

Analisis Komorbiditas dan Hubungannya dengan Tingkat Severitas Penyakit dan Mortalitas pada Pasien COVID-19 yang Dirawat di Rumah Sakit

Abstrak

Latar Belakang: *Komorbiditas merupakan faktor yang sangat penting dalam menentukan outcome dari COVID-19. Namun, studi yang telah ada terkait komorbiditas dan hubungannya dengan tingkat severitas COVID-19 dan mortalitas utamanya dibuat berdasarkan pengamatan pada komunitas, dan bukan pada mereka yang dirawat di rumah sakit. Studi ini bermaksud untuk mengamati dan menentukan profil demografik dari komorbiditas pada pasien-pasien COVID-19 yang dirawat di rumah sakit rujukan tersier dan hubungannya dengan tingkat severitas dan mortalitas.*

Metode: *Kami menganalisa data dari 60 pasien terkonfirmasi COVID-19 di rumah sakit kami di Kota Malang, Jawa Timur, dari Maret hingga Juni 2020. Kami menjabarkan profil demografik dari komorbiditas pada pasien kami dan melakukan analisa statistik untuk menentukan hubungannya dengan tingkat severitas penyakit dan mortalitas.*

Hasil: *Mayoritas dari sampel (66.7%) termasuk dalam kategori penyakit berat. 37 sampel (61.7%) mempunyai setidaknya satu komorbiditas. Tingkat mortalitas diantara sampel adalah 30% dan 37.8% pada kelompok sampel dengan komorbiditas. Komorbiditas dengan prevalensi tertinggi adalah hipertensi (40.0%), diikuti oleh gagal jantung (35.0%), dan diabetes (25.0%). Terdapat hubungan yang bermakna antara ada atau tidaknya komorbiditas dengan tingkat severitas penyakit dan antara tingkat severitas penyakit dan mortalitas ($p<0.05$). Diabetes merupakan satu-satunya komorbiditas dengan hubungan bermakna terhadap mortalitas pada studi kami ($p<0.05$; OR 4.0, 95% CI 1.16-13.74).*

Kesimpulan: *Pada pasien COVID-19 yang dirawat di rumah sakit, adanya komorbiditas berhubungan dengan tingkat severitas yang lebih berat dan mortalitas.* ***(J Respirol Indones 2022; 42(1): 18-25)***

Kata kunci: *komorbiditas; COVID-19; Tingkat severitas; Angka mortalitas*

Correspondence: Anthony Christanto
Email: tonychris@dr.com

INTRODUCTION

On December 31, 2019, China reported a mysterious case of pneumonia of unknown cause. Within three days, there were 44 patients with these cases, and the number continues to grow to this day, amounting to millions of cases. Isolates from patients were analyzed, and the findings revealed the presence of a new coronavirus infection, which was given the provisional name 2019 novel Coronavirus (2019-nCoV). On February 11, 2020, WHO named the new virus *Severe Acute Respiratory Syndrome Coronavirus*-2 (SARS-CoV-2) and the name of the disease Coronavirus Disease 2019 (COVID-19).[1]

In its development, WHO declared COVID-19 as a pandemic on March 11, 2020. This status determination was based on the fact that COVID-19 cases increased 13 times in two weeks, and the number of affected countries tripled. Despite the WHO recommendation that affected countries be "more aggressive", COVID-19 cases continued to increase as of June 9, 2020.[2] As a result, the number of COVID-19 cases worldwide has reached 7.222.353 and a mortality rate of 5.7%, much higher than the WHO's initial estimate of 2%.[3]

The COVID-19 Pandemic in Indonesia began on March 2, 2020, with the index case in Jakarta. The COVID-19 Pandemic expanded throughout Indonesia on April 9, 2020, with Jakarta, West Java, and East Java having the largest number of positive cases. Positive cases of COVID-19 in Indonesia totaled 33.076 as of June 9, 2020, with a mortality rate of 5.8%. East Java has eight regencies/cities identified as areas with local transmission (Kediri Regency, Malang Regency, Sidoarjo Regency, Magetan Regency, Gresik Regency, Malang City, Surabaya City, and Batu City).[4]

Previous studies have shown that COVID-19 patients with comorbidities have a poorer prognosis.[5] Wang et al. found that in 138 cases of COVID-19, 64 (46.4%) of them had comorbidities. Patients admitted to the intensive care unit had a higher comorbidity rate (72.2% vs. 37.3%) than those who were not admitted to the intensive care unit. It suggests that comorbidity may be an important risk factor for *outcome* in patients with COVID-19.[6]

This study aims to determine the distribution of comorbidities in patients treated in the PINERE treatment room, Dr. Saiful Anwar Malang Hospital and analyze its relationship with the level of severity and mortality.

METHODS

The design of this research is observational analytic with a cross-sectional approach. The research was conducted at Dr. Saiful Anwar Malang Hospital in April – June 2020. The inclusion criteria were all confirmed COVID-19 patients either through the SARS-CoV-2 Rapid Molecular Test (RMT) method using the GeneXpert® SARS-CoV-2 method or the real-time Polymerase Chain method Reaction (rt-PCR), which was treated in the PINERE Room, Dr. Saiful Anwar Malang Hospital from March 12 to June 5 2020. The research data is in the form of secondary data taken from medical records.

The patient's diagnosis determines comorbidity during treatment. In this study, eight types of comorbidities were investigated, namely "Age", defined as patients aged 60 years or older according to WHO criteria for the elderly; "COPD", defined as a patient with a clinical manifestations of COPD, radiological features supporting COPD, or a history of a previous diagnosis of COPD. “Diabetes Mellitus”, defined as a patient with a history of the previous diagnosis of diabetes mellitus (type 1 and type 2), random blood glucose at admission >200 mg/dL with classic complaints, fasting blood sugar above 126 mg/dL, postprandial blood sugar 200 mg/dL, or HbA1C values above 6.5%. “Hypertension”, defined as a patient with a blood pressure measurement above 130 mmHg for 2 consecutive times with a distance of at least 2 minutes and/or a history of a previous diagnosis of hypertension.

“Heart failure”, defined as a patient with typical symptoms of heart failure (shortness of breath at rest or activity, fatigue, leg oedema) and typical signs of heart failure (tachycardia, tachypnea, pulmonary rales, pleural effusion, elevated jugular venous

pressure, peripheral oedema, hepatomegaly), as well as objective signs of structural or functional disturbances of the heart at rest, cardiomegaly, third heart sound, heart murmur, abnormalities in echocardiography, and increased concentrations of natriuretic peptides (according to the 2015 Guidelines for Management of Heart Failure of the Indonesian Cardiovascular Specialist Association (PERKI).

"Coronary artery disease", defined as a patient with classic symptoms of angina pectoris accompanied by other findings such as electrocardiography and cardiac enzymes suggestive of coronary artery disease according to the cardiologist's expertise. "Chronic Kidney Disease" or “CKD”, defined as a patient with a clinical picture of CKD accompanied by decreased renal function or a history of a previous diagnosis of CKD; and “Cerebrovascular disease” is defined as the presence of clinical and/or radiological features suggestive of a cerebrovascular disorder or a sequela of cerebrovascular disease.

The severity of the disease is grouped into mild, moderate, and severe according to the division listed in the Guidelines for Prevention and Control of Coronavirus Disease-19 (COVID-19) published by the Director-General of P2P of the Ministry of Health of the Republic of Indonesia version 4, where "Mild" include fever >38^{o}C, cough, sore throat, nasal congestion, and malaise, without symptoms of pneumonia; "Moderate" include the above symptoms plus shortness of breath; and "Severe" include persistent fever >38^{o}C plus symptoms of severe ARI or pneumonia (including respiratory rate >30 breaths/minute, severe respiratory distress, or oxygen saturation < 90% in room air).

We described the distribution of confirmed COVID-19 patients based on disease severity, comorbidities, and mortality (died/did not die). Then, statistical tests were carried out to see whether or not there was an association between the presence or absence of comorbidities with patient severity and mortality rates and whether there was an association between severity and patient mortality using IBM SPSS® 25 software.

RESULT

From a total of 60 research samples, the following results were obtained: According to the severity of the disease, 40 samples (66.7%) were categorized as severe symptoms, 14 samples (23.3%) were categorized as moderate symptoms, and six samples (10.0%) were categorized as mild symptoms. In addition, 37 samples (61.7%) had comorbidities, with details of 21 samples (56.8%) with two or more comorbidities (multiple comorbidities) and 16 samples (43.2%) with single comorbidities. The mortality rates were 18 samples (30.0%) in the total sample, 14 samples (37.8%) in the comorbid sample, six samples (37.5%) in the single comorbid sample, eight samples (38.1%) in the multiple comorbid samples, and four samples (17.4%) in samples without comorbidities.

According to comorbidity, a total of 20 samples (33.3%) had comorbid age or were 60 years or older. In addition to age comorbidity, the highest comorbidity rate was hypertension, which was 24 samples (40.0%), followed by heart failure in 21 samples (35.0%), diabetes mellitus in 15 samples (25.0%), COPD and coronary heart disease each with several four samples (6.7%). There were no samples with chronic kidney disease and cerebrovascular disease.

The statistical test that used is the Fischer's Exact test and found a significant relationship between the presence or absence of comorbidities and the severity level (P<0.05), a significant relationship between sample severity and mortality (P<0.05). Statistical analysis of comorbidities using logistic regression showed that there was no relationship between comorbidity and severity. Still, there was a relationship between comorbid diabetes mellitus and mortality (P<0.05; OR=4.00; 95% CI=1.16–13.74). The sample analysis with mortality (18 samples) found that 17 samples (94.4%) came with the category of severe symptoms. In addition, 14 samples (77.8%) had comorbidities, with details of six samples (33.3%) with single comorbidities and eight samples (44.4%) with multiple comorbidities (two or more comorbidities).

Tablel 1. Demographic Profile

Variable		N (%)
Presence or no Comorbid (n=60)	At least one comorbid	37 (61.7%)
	No comorbid	23 (38.3%)
Number of comorbidities in samples with comorbidities (n=37)	Single	16 (43.2%)
	Multiple	21 (56.8%)
Age (n=60)	60 years or older	20 (33.3%)
	Less than 60 years old	40 (66.7%)
Mortality Rate		
On all samples (n=60)	Yes	18 (30.0%)
	No	42 (70.0%)
In samples with comorbidities (n=37)	Yes	14 (37.8%)
	No	23 (62.2%)
In samples with a single comorbid (n=16)	Yes	6 (37.5%)
	No	10 (62.5%)
In samples with multiple comorbidities (n=21)	Yes	8 (38.1%)
	No	13 (61.9%)
In samples without comorbid (n=23)	Yes	4 (17.4%)
	No	19 (82.6%)
In the sample aged 60 years or older (n=20)	Yes	9 (45.0%)
	No	11 (55.0%)
In the sample aged less than 60 years (n=40)	Yes	9 (22.5%)
	No	31 (77.5%)
Severity Level		
On all samples (n=60)	Mild	6 (10.0%)
	Moderate	14 (23.3%)
	Heavy	40 (66.7%)
In samples with comorbidities (n=37)	Mild	1 (2.7%)
	Moderate	8 (21.6%)
	Heavy	28 (75.7%)
In samples with a single comorbid (n=16)	Mild	0 (0.0%)
	Moderate	4 (25.0%)
	Heavy	12 (75.0%)
In samples with multiple comorbidities (n=21)	Mild	1 (4.8%)
	Moderate	4 (19.0%)
	Heavy	16 (76.2%)
In samples without comorbid (n=23)	Mild	5 (21.7%)
	Moderate	6 (26.1%)
	Heavy	12 (52.2%)
In the sample aged 60 years or older (n=20)	Mild	1 (5.0%)
	Moderate	3 (15.0%)
	Heavy	16 (80.0%)
In the sample aged less than 60 years (n=40)	Mild	5 (12.5%)
	Moderate	11 (27.5%)
	Heavy	24 (60.0%)
Comorbidities (other than age)		
Hypertension (n=60)	Yes	24 (40.0%)
	No	36 (60.0%)
Heart failure (n=60)	Yes	21 (35.0%)
	No	39 (65.0%)
Diabetes(n=60)	Yes	15 (25.0%)
	No	45 (75.0%)
COPD (n=60)	Yes	4 (6.7%)
	No	56 (93.3%)
Coronary artery disease (n=60)	Yes	4 (6.7%)
	No	56 (93.3%)
Chronic kidney disease (n=60)	Yes	0 (0.0%)
	No	60 (100.0%)
Cerebrovascular disease (n=60)	Yes	0 (0.0%)
	No	60 (100.0%)

The highest comorbidities in the sample group with mortality were age and hypertension, each with nine samples (50.0%), followed by diabetes mellitus in eight samples (44.4%), heart failure in seven samples (38.9%) and COPD in two samples (11.1%).

Table 2. Table of contingency to the level of severity

Variable		Severity Level			*P*
		Mild	Moderate	Heavy	
Presence of comorbid	Yes (n=37)	1 (2.7%)	8 (21.6%)	28 (75.7%)	0.037
	No (n=23)	5 (21.7%)	6 (26.1%)	12 (52.2%)	
Number of comorbids	Single (n=16)	0 (0.0%)	4 (25.0%)	12 (75.0%)	0.202
	Multiple (n=21)	1 (4.8%)	4 (19.0%)	16 (76.2%)	
	No comorbid (n=23)	5 (21.7%)	6 (26.1%)	12 (52.2%)	
Age	60 years or older (n=20)	1 (5.0%)	3 (15.0%)	16 (80.0%)	0.358
	Less than 60 years old (n=40)	5 (12.5%)	11 (27.5%)	24 (60.0%)	
COPD	Yes (n=4)	0 (0.0%)	1 (25.0%)	3 (75.0%)	1.000
	No (n=56)	6 (10.7%)	13 (23.2%)	37 (66.1%)	
Diabetes	Yes (n=15)	1 (6.7%)	3 (20.0%)	11 (73.3%)	0.904
	No (n=45)	5 (11.1%)	11 (24.4%)	29 (64.4%)	
Hypertension	Yes (n=24)	1 (4.2%)	5 (20.8%)	18 (75.0%)	0.468
	No (n=36)	5 (13.9%)	9 (25.0%)	22 (61.1%)	
Heart Failure	Yes (n=21)	1 (4.8%)	5 (23.8%)	15 (71.4%)	0.769
	No (n=39)	5 (12.8%)	9 (23.1%)	25 (64.1%)	
Coronary artery disease	Yes (n=4)	0 (0.0%)	1 (25.0%)	3 (75.0%)	1.000
	No (n=56)	6 (10.7%)	13 (23.2%)	37 (66.1%)	
Chronic kidney disease	Yes (n=0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
	No (n=60)	6 (10.0%)	14 (23.3%)	40 (66.7%)	
Cerebrovascular disease	Yes (n=0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
	No (n=60)	6 (10.0%)	14 (23.3%)	40 (66.7%)	

Table 3. Contingency Table on Mortality

Variable		Mortality		*P*
		Yes	No	
Presence of comorbid	Yes (n=37)	14 (37.8%)	23 (62.2%)	0.147
	No (n=23)	4 (17.4%)	19 (82.6%)	
Number of comorbids	Single (n=16)	6 (37.5%)	10 (62.5%)	0.253
	Multiple (n=21)	8 (38.1%)	13 (61.9%)	
	No comorbid (n=23)	4 (17.4%)	19 (82.6%)	
Severity level	Mild (n=6)	0 (0.0%)	6 (100.0%)	0.012
	Moderate (n=14)	1 (7.1%)	13 (92.9%)	
	Heavy (n=40)	17 (42.5%)	23 (57.5%)	
Age	60 years or older (n=20)	9 (45.0%)	11 (55.0%)	0.134
	Less than 60 years old (n=40)	9 (22.5%)	31 (77.5%)	
COPD	Yes (n=4)	2 (50.0%)	2 (50.0%)	0.576
	No (n=56)	16 (28.6%)	40 (71.4%)	
Diabetes	Yes (n=15)	8 (53.3%)	7 (46.7%)	0.048
	No (n=45)	10 (22.2%)	35 (77.8%)	(OR 4.0 95% CI 1.16-13.74)
Hypertension	Yes (n=24)	9 (37.5%)	15 (62.5%)	0.391
	No (n=36)	9 (25.0%)	27 (75.0%)	
Heart failure	Yes (n=21)	7 (33.3%)	14 (66.7%)	0.771
	No (n=39)	11 (28.2%)	28 (71.8%)	
Coronary artery disease	Yes (n=4)	0 (0.0%)	4 (100.0%)	0.306
	No (n=56)	18 (32.1%)	38 (67.9%)	
Chronic kidney disease	Yes (n=0)	0 (0.0%)	0 (0.0%)	-
	No (n=60)	18 (30.0%)	42 (70.0%)	
Cerebrovascular disease	Yes (n=0)	0 (0.0%)	0 (0.0%)	-
	No (n=60)	18 (30.0%)	42 (70.0%)	

DISCUSSION

Currently, COVID-19 has become a global pandemic. The number of cases worldwide continues to increase and currently has reached more than 7 million cases. In Indonesia, the number of COVID-19 cases has reached more than 30,000 in just 3 months since the first case was discovered, with a mortality rate of around 5.8%. This figure is not much different from the global mortality rate, which is around 5.7%.[3]

According to the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) report, approximately 80% of patients with confirmed COVID-19 exhibit only mild-moderate symptoms, with just about 14% developing severe symptoms.[7] In contrast, data at our hospital showed that most of the samples (66.7%) had severe symptoms. This is natural considering that, as a tertiary referral hospital, the COVID-19 patients admitted to our hospital cannot be treated in other smaller satellite COVID-19 hospitals. It may also explain our sample's mortality rate, which is much higher than the national average (30.0% vs. 5.8%).

Comorbidity is a very important factor in determining the *outcome* of COVID-19. The studies conducted by Guan et al. and Wang et al. stated that comorbid COVID-19 patients had a poorer prognosis. Therefore, the presence and number of comorbidities could predict the clinical outcomes of COVID-19.[5,6,8] A large-scale study of 1.590 patients in China put the comorbidity rate at 25.1%,[8] and in Indonesia, provisional data from 2.171 cases showed the comorbidity rate was 30.68%.[9]

Our sample had a much higher comorbidity rate of 61.7%. This may be explained by the severity of the patient's condition when referred to our hospital, where we found an association in our sample between comorbidity and severity. This follows most studies showing that comorbidities will increase the risk of a person with COVID-19 having a more severe form of the disease and the possibility of mortality.[5,7] Our study also showed that mortality rate in the sample with comorbidities was much higher than in the sample without comorbidities (37.8% vs. 17.4%).

Based on the comorbidity profile, excluding age, we found that the highest number of comorbidities was hypertension (40.0%), followed by heart failure (35.0%), diabetes mellitus (25.0%), and COPD and coronary heart disease (6.7% each). We did not find any samples with comorbid chronic kidney disease and cerebrovascular disease. This profile is similar to the comorbidity profile reported by Guan et al., namely hypertension as the most frequent comorbidity (16.9%), followed by diabetes mellitus (8.2%) and cardiovascular disease (3.7%). Cerebrovascular disease and chronic kidney disease account for only a small percentage of these comorbidities (1.9% and 1.5%).[8]

From the analysis of each comorbidity, only diabetes mellitus comorbidity has a significant relationship to mortality. People with diabetes mellitus tend to die four times more often than those without diabetes. This value is two times bigger than the hazard ratio of diabetes mellitus to mortality reported by Guan et al.[8]

Guan et al. also showed that patients with two or more comorbidities had a much more significant mortality risk.[8] In our data, the mortality rate in the single comorbid sample was not significantly different from that of the multiple comorbid samples (37.5% vs. 38.1%). This was also seen in the sample with severe severity (75.0% in the single comorbid sample vs. 76.2% in the multiple comorbid samples). Djaharuddin et al. showed a hazard ratio of 1.79 (95% CI) in patients with two or more comorbidities compared with those at least two comorbidities.[10]

We also analyzed the samples with mortality and found that 94.4% of the samples who died were treated with severe symptoms, and most had comorbidities (77.8%). On the other hand, this shows that 22.2% of the sample died even though they did not have any comorbidities. Furthermore, half of those who died (50.0%) were 60 or older or had comorbid hypertension.

Existing studies show that the mortality rate increases significantly with age.[6,11] In our sample, we found that the mortality rate in the sample aged 60 years or older was 45.0% and 22.5% in the sample aged less than 60 years. This is consistent with

existing studies showing that the risk of mortality from COVID-19 increases exponentially with age. In their study, Djaharuddin et al. showed that the mortality rate occurred most in the elderly group. This is thought to be caused by the tendency of the elderly to develop cytokine storms due to immunosenescence.[10]

Our data, therefore, is consistent with most studies that state either hypertension or diabetes as comorbidities that may have been the most impactful in increasing mortality rates in COVID-19 patients. It should be noted, however, that a significant amount of mortality occurs in those who have no comorbidities at all.[12,13]

CONCLUSION

From the data we have obtained and its analysis, we conclude that the demographic profile of hospitalized COVID-19 patients (especially those in central referral hospitals) will be different from the demographic profile of COVID-19 sufferers in the community. Although the current demographic profile is drawn from most studies based on general community observations that include COVID-19 patients requiring treatment and those with mild disease, using this data as a basis for making clinical decisions in treating COVID-19 in the hospital would be irrelevant. For example, in our study, the number of comorbidities (single vs multiple) was less likely to have a significant association with the outcome than COVID-19. This indicates that the number of comorbidities that patients have may not be clinically significant in those hospitalized. This is undoubtedly in contrast to the findings of earlier research, which clearly demonstrated that the number of comorbidities had a significant impact on the outcome of COVID-19.

The presence of comorbidities remains a factor that influences the disease course of COVID-19, especially its severity and mortality, as the available data consistently show. However, we propose that when treating hospitalized COVID-19 patients, clinicians should consider that the absence of comorbidities is not directly associated with a better prognosis. It was observed that some of the patients with mortality in our study had no comorbidities at all.

REFERENCES

1. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. World Health Organization. 2020 [cited 2020 Aug 13]. 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
2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta bio-medica Atenei Parm. 2020;91(1):157–60.
3. World Health Organization. Update on the situation regarding the new coronavirus [Internet]. World Health Organization. 2020 [cited 2020 Jan 29]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?adgroupsurvey=%7Badgroupsurvey%7D&gclid=CjwKCAiA9aKQBhBREiwAyGP5lbJhBLYvL4aPp_BpK6NhpGHDlB0yNpbHl_X5KD1ySjS0RPfL2j3sGBoCQMsQAvD_BwE
4. Kementrian Kesehatan Republik Indonesia. Infeksi Emerging Kementerian Kesehatan RI [Internet]. Kementrian Kesehatan Republik Indonesia. 2020 [cited 2020 Jun 9]. Available from: https://infeksiemerging.kemkes.go.id/
5. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.
7. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). World Health Organization. China; 2020.

8. Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547.
9. Kementerian Kesehatan Republik Indonesia. COVID-19 dalam Angka per 3 Juni 2020 [Internet]. Kementerian Kesehatan Republik Indonesia. 2020 [cited 2020 Jun 4]. Available from: https://www.kemkes.go.id/article/view/20060600001/covid-19-dalam-angka-per-6-juni-2020.html
10. Djaharuddin I, Munawwarah S, Nurulita A, Ilyas M, Tabri NA, Lihawa N. Comorbidities and mortality in COVID-19 patients. Gac Sanit. 2021;35 Suppl 2:S530–2.
11. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ. 2020 Mar;368:m1198.
12. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020;13(12):1833–9.
13. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5.

Correlation between N-Acetyltransferase 2 (NAT2) Polymorphism Genotype with Plasma Isoniazid (INH) Concentration in MDR TB Patients Receiving Short Regimen in West Sumatera

Mega Senja, Masrul Basyar, Yessy Susanty Sabri, Afriani

Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Andalas, Padang

Abstrak

Background: *Isoniazid (INH) is one of the most potent TB drug. High dose INH is used in short regimen MDR TB drugs. The genetic polymorphism of NAT2 affects the acetylation status. Awareness of the patients' acetylator status is important to determine the risk of toxicity, treatment failure and drug resistance. The aim of this study was to demonstrate NAT2 genotype association with INH plasma concentration after 2 hours of oral INH therapy.*

Methods: *This was a cross sectional study of MDR TB patients who received short term combination therapy at RSUP Dr. M.Djamil Padang, Achmad Muchtar Hospital Bukittinggiand West Sumatra Pulmonary Hospital from September 2019 to February 2020. Patients were examined for NAT2 genotype and plasma INH concentration. The results of the plasma INH concentrations obtained were evaluated based on the NAT2 acetylator phenotype group.*

Results: *The majority of the subjects weremen (62.5%), aged 40-64 years (50%), had the most common comorbid of diabetes mellitus (31.25%), were normoweight (75%) and had negative HIV status (93.8%). A total of 7 alleles consisting of 7 SNPs and 7 variations of the NAT2 genotype were found in MDR TB patients who received short-term therapy. The NAT2*12A alleles (56.25%) was the most common allele and was a fast acetylator. Based on the bimodal distribution, the median concentration of INH in the fast and slow acetylator were 1.25 µg/ml and 5.24 µg/ml, respectively. The median values of INH concentration based on the trimodal distribution for fast, intermediate, and slow acetylators were 1.25 µg/ml, 2.17 µg/ml and 5.24 µg/ml.*

Conclusion: *There were no correlations between the type of NAT2 acetylator phenotype and plasma INH concentrations. (**J Respirol Indones 2022; 42(1): 26-33)***

Keywords: *NAT2, INH, polymorphism, MDR TB*

Hubungan Polimorfisme Genotip N-Acetyltransferase 2 (NAT2) dengan Konsentrasi Isoniazid (INH) Plasma pada Pasien TB yang Mendapat Paduan Terapi Jangka Pendek di Sumatera Barat

Abstrak

Latar belakang*: Isoniazid (INH) adalah salah satu obat TB yang paling ampuh. INH dosis tinggi digunakan pada paduan terapi TB MDR jangka pendek. Polimorfisme genetik NAT2 berpengaruh terhadap status asetilasi. Pengetahuan mengenai status asetilator pasien penting untuk menilai risiko toksisitas, kegagalan pengobatan dan resistensi obat. Penelitian ini bertujuan mengetahui hubungan polimorfisme genotip NAT2 dengan konsentrasi plasma INH 2 jam setelah pemberian INH oral.*

Metode: *Penelitian potong lintang pada pasien TB MDR yang mendapat paduan terapi jangka pendek di RSUP Dr. M.Djamil Padang, RS Achmad Muchtar Bukittinggi dan RS Paru Sumatera Barat dari September 2019 hingga Februari 2020. Pasien diperiksa genotip NAT2 dan konsentrasi INH plasma. Hasil konsentrasi INH plasma yang didapatkan dievaluasi berdasarkan kelompok fenotip asetilator NAT2.*

Hasil:*Sebagian besar subjek penelitian adalah laki-laki (62,5%) berusia 40-64 tahun (50%), komorbid terbanyak ditemukan diabetes mellitus (31,25%), berstatus* normoweight*(75%) dan status HIV negatif (93,8%). Sebanyak 7 alel yang terdiri dari 7 SNP dan 7 variasi genotipe NAT2 ditemukan pada pasien TB MDR yang mendapat terapi jangka pendek. Alel NAT2*12A (56,25%) merupakan alel yang paling sering ditemukan dan merupakan asetilator cepat. Berdasarkan distribusi bimodal nilai tengah konsentrasi INH pada asetilator cepat dan lambat adalah 1,25µg/ml dan 5,24µg/m. Nilai tengah konsentrasi INH berdasarkan distribusi trimodal untuk asetilator cepat, menengah dan lambat secara berurutan adalah 1,25 µg/ml, 2,17µg/ml dan 5,24µg/ml.*

Kesimpulan: *Tidak ada hubungan antara jenis fenotip asetilator NAT2 dengan konsentrasi INH plasma. (**J Respirol Indones 2022; 42(1): 26-33)***

Kata kunci: *NAT2, INH, Polimorfisme, TB MDR*

Correspondence: Mega Senja
Email: dr.megasenja@gmail.com

INTRODUCTION

Indonesia is a country with the third-highest burden of Tuberculosis (TB) globally after India and China. One of the challenges faced today is the increasing number of drug-resistant TB cases. Multi Drug-Resistant Tuberculosis (MDR TB) is defined as TB that is resistant to at least two main anti-tuberculosis drugs, namely isoniazid (INH) and rifampin with or without other first-line drugs. According to the 2018 WHO Global Report, it was estimated that there were 558,000 cases of MDR TB worldwide. Indonesia itself ranks 10th in the incidence of MDR TB worldwide.[1]

In 2016 WHO began to recommend using a short-term regimen for the management of MDR-TB under certain conditions.[2] One of the drugs used in the short-term regimen is high-dose INH. Awareness of the acetylation status can help to decide which dose of INH to be used because treatment efficacy and INH toxicity are associated with increased metabolism (acetylation) in specific individuals, as determined by mutations in the NAT2 gene.[3]

INH has been an important component used for TB treatment since the early 1950s until now. The advantages of INH are effective against TB, affordable price, easy to digest, and well absorbed withthe maximum plasma concentration occurs 2 hours after administration. INH in the body is metabolized by the arylamine NAT2 enzyme, whose activity is influenced by genetic variations (polymorphisms).[4] This variation is responsible for plasma drug levels and drug half-life.[3]

Based on its ability to metabolize INH, the phenotype of the NAT2 gene can be categorized into distributions: bimodal and trimodal distributions. The bimodal distribution consists of fast acetylator and slow acetylator, while the trimodal distribution consists of fast acetylator, intermediate acetylator, and slow acetylator. The global distribution of NAT2 indicates that 15–40% of the world's population has a slow acetylator phenotype.[5] In Indonesia alone; a study conducted by Yuliwulandari, et al. on 212 people (Javanese and Sundanese ethnicity) found that the frequency of fast acetylator phenotype was 13.6%, intermediate acetylator of 50.8%, and slow acetylatorof 35.6%. The frequency of NAT2 genotype can vary between different ethnicities.[6]

A study conducted by Singh, et al. on 201 TB patients obtained a significant difference (P<0.001) between the variation of NAT2 genotype and plasma INH concentration. In this study, the fast acetylator group (13%) had a mean 2-hour plasma INH concentration of 2.4 µg/ml, the intermediate acetylator (32%) had a mean value of 4.1 µg/ml, while slow acetylator (55%) had 5.6 µg/ml.[7] Another study by Zabost, et al. on 130 patients found plasma INH concentrations for 3 hours in the fast (5.4%), intermediate (30%), and slow (64.4%) acetylator groups. were 1.2±0.6 µg/ml, 2.2±1.3 µg/ml and 4.4±1.5 µg/ml, respectively.[8]

Another study by Kumar, et al. in India regarding the genetic variation of NAT2 with 2-hours plasma INH concentration revealed that the median values in the three acetylator groups were significantly different, namely in the fast acetylator group (58%) had a median INH value of 10.2 µg/ml, the slow acetylator group (35%) had 8.1 µg/ml, while the intermediate acetylator group (23%) had 4.1 µg/ml.[9]

Study on NAT2 gene polymorphisms of TB patients in Indonesia, especially MDR TB, has not been widely carried out. The MDR TB combination treatment currently uses a short-term regimen, one of which is using high-dose INH drugs. Therefore, researchers are interested in investigating the polymorphism of the NAT2 gene and assessing INH levels based on their genotype in each MDR TB patient who received a standard short-term regimen at the MDR TB referral hospital in West Sumatra.

METHODS

This was a cross-sectional study of all MDR TB patients who received short-term combination therapy at RSUP Dr. M.Djamil Padang, Achmad Muchtar Hospital Bukittinggi, and West Sumatra Pulmonary Hospital from August 2019 to February 2020. The inclusion criteria were MDR TB patients on short-term intensive phase treatment for at least

4 weeks, aged >17 years, and willing to participate in the study by signing the consent form after receiving an explanation.

The analysis in this study consisted of univariate and bivariate analysis. Univariate analysis was carried out to determine the frequency distribution of MDR TB patients' characteristics and genotypic polymorphisms in MDR TB patients who received short-term regimens. In addition, an analysis was also carried out to see the mean and median plasma INH concentrations after 2 hours of administration. Bivariate analysis was performed using the Kruskal Wallis test for the trimodal group and the Mann-Whitney test for the bimodal group to examine the correlation between NAT2 genotypic polymorphisms and plasma INH concentrations after 2 hours.

RESULTS

This study analyzed data from a total of 16 patients. The characteristics of the patients were mostly male (62.50%), with the highest age group of 40–64 years old. Most of the patients (75%) were normoweight (BMI 18.5–24.9%). Subjects with comorbid of diabetes mellitus were 31.25%, however, only 1 subject with HIV (6.25%) was found. Rapid molecular testof most patients resulted in medium detectable MTB (Table 1).

Sequencing analysis could be performed on 16 samples. There were 7-point mutations (SNP). The combination of SNPs produced 7 different alleles which carried acetylator properties. The most common allele found was NAT2*12A (56.25%) which had a point mutation of 803 A>G (rs1208) and moved withfast acetylation properties. One sample had a mutation at point 341 T>C 776C>A 803 G>A. The mutation at point 776 C>A had not been published in the NAT2 database (accessible at http://nat.mbg.duth.gr), so the allele type has not been determined (Table 2).

In this study, the phenotype predictionwas divided based on the distribution of trimodal (fast acetylator, intermediate acetylator and slow acetylator) and bimodal (fast and slow acetylators). The acetylator phenotype is a combination of two alleles.

Based on trimodal phenotype predictions, the most common phenotypes found in this study were fast acetylators (62.5%) namely NAT2*4/*4, NAT2*12A/*12A; intermediate acetylators (12.50%) namely NAT2*12B/NAT2*12B, NAT2*6C/*12B; and slow acetylators (18.75%) namely NAT2*6C/*6C, NAT*5A/*5A, NAT2*7C/*7C. Meanwhile, 75% of fast acetylator and 18.75% of slow acetylator were found based on the bimodal distribution. There was 1 sample (6.25%) whose acetylator phenotype was unknown. Since it was unknown, the data was published in the NAT2 database (accessible at http://nat.mbg.duth.gr) so that the type of acetylator could not be determined (Table 3).

Table 1. Characteristics of MDR-TB patients receiving short-term regimen in West Sumatra.

Characteristic	Total (N)	Frequency (%)
Gender		
Male	10	62.5
Female	6	37.5
Age		
18–39 years	7	43.8
40–64 years	8	50.0
≥65 years	1	6.2
Body Mass Index		
Underweight (BMI<18.5)	4	25
Normoweight (18.5–24.9)	12	75
Comorbidity		
Diabetes mellitus	5	31.2
No comorbid	11	68.8
HIV Status		
Positive	1	6.2
Negative	15	93.8

All samples were examined for plasma INH levels 2 hours after drug administration. The median value of INH levels in the fast acetylator group was 1.25 µg/ml, the intermediate acetylator group of 2.17 µg/ml, and the slow acetylator groupof 5.24 µg/ml (Table 4). Meanwhile, based on a bimodal distribution, the median value of isoniazid levels in the fast acetylator group was 1.25 µg/ml, and in the slow acetylator group was 5.24 µg/ml (Table 4, Table 5).

Table 2. Distribution and frequency of NAT2 allele polymorphisms in MDR TB patients receiving short-term regimen in West Sumatra

Combines SNP (Haplotype)							NAT2 Allele	Prediction Phenotype	Allele Total (n)	Allele Frequency (%)
282 C>T (rs1041983)	341 T>C (rs1801280)	481 C>T (rs1799929)	590 G>A (rs1799930)	803 A>G (rs1208)	857 G>A (rs1799931)	776 C>A (rs1304162037) **				
C	T	C	G	A	G	C	NAT2*4	Fast Acetylator	2	6.25
C	C*	T*	G	A	G	C	NAT2*5A	Slow Acetylator	2	6.25
T*	T	C	A*	G*	G	C	NAT2*6C	Slow Acetylator	3	9.375
T*	T	C	G	G*	A*	C	NAT2*7C	Slow Acetylator	2	6.25
C	T	C	G	G*	A	C	NAT2*12A	Fast Acetylator	18	56.25
T*	T	C	G	G*	G	C	NAT2*12B	Fast Acetylator	3	9.375
C	C	C	G	A	G	A	Others	Unknown	2	6.25

Note: * Known and published SNPs; ** Unpublished SNP

Table 3. Distribution of NAT2 genotypes and prediction of acetylator phenotype

No	Genotype	Total	%	Phenotype Prediction			
				Trimodal distribution	%	Bimodal Distribution	%
1	NAT2*4/*4	1	6.25	Rapid	62.50	Rapid	75
2	NAT2*12A/*12A	9	56.25	Rapid		Rapid	
3	NAT2*12B/*12B	1	6.25	Intermediate	12.50	Rapid	
4	NAT*6C/12B	1	6.25	Intermediate		Rapid	
5	NAT*6C/*6C	1	6.25	Slow	18.75	Slow	18.75
6	NAT2*5A/*5A	1	6.25	Slow		Slow	
7	NAT2*7C/*7C	1	6.25	Slow		Slow	
8	Unknown	1	6.25	-		-	

Table 4. INH concentration after 2 hours of administration based on trimodal distribution

Variable	Fast Acetylator (n=10)	Intermediate Acetylator (n=2)	Slow Acetylator (n=3)
INH concentration (µg/ml)	1.25 (0–8.50)	2.17 (0–4.33)	5.24 (0.25–14.16)

Table 5. INH concentrations after 2 hours of oral administration in MDR TB patients based on bimodal group phenotype

Variable	Fast Acetylator (n=12)	Slow Acetylator (n=3)
INH concentration	1.25 (0–8.50)	5.24 (0.25–14.16)

Table 6. Correlation of INHlevels in the bimodal and trimodal group

Variable	Median	Min-Max	*P*
INH level	1.56	0–14.16	0.448
Bimodal	1.00	1–2	
INH level	1.56	0–14.16	0.598
Trimodal	1.00	1–3	

This study correlated the NAT2 genotypic polymorphism with INH concentration after 2 hours of oral administration in MDR TB patients based on the acetylator phenotype (bimodal and trimodal). The results showed that there were no correlations between INH levels in the trimodal group (*P*=0.598) as seen in Table 6.

DISCUSSION

Most of MDR TB patients who received short-term intensive phase therapy in this study were male (62.50%), with the highest age group being 40-64 years (50%), comorbid of diabetes mellitus (31.25%), and had normal BMI (75%). Several studies have obtained results that were not much different from this study. Pradipta, et al. reported that most of MDR TB patients who received short-term therapy at the Persahabatan Hospital (61.5%) were male with the age range being 41-50 years, had comorbid of diabetes mellitus (30.8%) but was dominated by subjects with underweight BMI status (32.7%).[10]

The NAT2 genotype polymorphism affects the acetylation status. The correlation between the acetylation phenotype and the NAT2 genotype has been reported in several studies.[11,12] In this study,

we obtained 7 different SNPs and there were 7 variations of SNP/polymorphism of the NAT2 genotype based on the results of the coding region sequencing, namely rs1041983, rs1801280, rs1799929, rs1799930, rs1208, rs1799931, and rs1304162037. Point mutations cause polymorphisms of the NAT2 gene (SNPs) in nucleotides, and their combinations produce different alleles.[13]

The allele variations in this study, namely NAT2*4, NAT2*5A, NAT2*6C, NAT2*7C, NAT2*12A, and NAT2*12B, were adjusted according to the guidelines of The Arylamine N-acetyltransferase Gene Nomenclature Committee accessed at http://nat.mbg.duth.gr/Human%20NAT2%20alleles_2013.htm. The alleles NAT2*4, NAT2*12A, NAT2*12B carry fast acetylator properties, while NAT2*5A, NAT2*6C, and NAT2*7C are carriers for slow acetylator properties.[13]

In this study, the NAT2*12A allele was the dominant allele (56.25%), followed by NAT2*5A (12.50%) and NAT2*6C (9.375%), while the other allele frequencies were <10%. The NAT2*4 allele is the reference allele or called the wild-type allele because no mutation was found.[14] In this study, the frequency was 6.225%. This finding was different from the study of Yuliwulandari, et al. who reported the frequency of the NAT2*4 allele was 36.9% and was the dominant allele. In contrast, the NAT2*12A allele was lower than the current study, which was <2% (0.8%).[15] Susilowati, et al. reported that the dominant allele was NAT2*6A (38%), while the NAT2*12A allele in that study was only 4%.[16] Study from Patin, et al. reported the frequency of NAT2*5B allele was 23.3%, NAT2*12A of 22.6%, and NAT2*6A of 18.6%.[17]

In previous studies in China, Japan, Indonesia, and Thailand, the NAT2*4 and NAT2*6 alleles were the most common.[15] In this study, new allele variations were found and were not reported in the NAT2 nomenclature database. The allele was mutated at 341 T>C, 776 C>A (rs1304162037), and 823 T>A (rs14856670). Based on the NAT2 gene data accessed at http://asia.ensembl.org, it was found that the point mutation 776 C>A (rs1304162037) was only released in April 2020, and there has been no publication so that the type of allele for this mutation could not be determined.[18]

The frequency of allele variations found in various studies was caused by variations in the NAT2 phenotype in different ethnic groups. The variations in some of the studies above may be due to differences in the ethnicity of the research subjects, such as this study that was conducted in West Sumatra, dominated by the Minang ethnic, study from Yuliwandari was conducted on the Javanese and Sundanese, study from Susilowati on the Indonesian Malay ethnicity and the study of Patin, et al. in the African population.[15–17] Variation can be caused by natural mutations, demographic influences, the influence of food consumed, and the influence of lifestyle as reported by Sabbagh et al. A study of the NAT2 gene variation in six Central Asian populations revealed clear differences between populations with different lifestyles and eating habits, which in this study were found to be slow acetylators in sedentary farmers (55–63%) compared to herders.[19]

Based on the bimodal distribution group, the frequency of the acetylator phenotype in this study was 75% fast acetylator and 18.75% slow acetylator while based on the trimodal distribution, the frequency of the acetylator phenotype in this study was 62.50% fast acetylator, intermediate acetylator 12.50% and 18.75% slow acetylator. The details of the combination of fast acetylator alleles (phenotypes) in this study are NAT*12A/NAT2*12A, NAT2*4/NAT2*4, NAT2*12B/NAT2*12B, NAT2*6C/NAT2*12B) and acetylators (NAT2*6C/NAT2*6C, NAT2*5A/NAT2*5A, NAT2*7C/NAT2*7C). In general, the dominant phenotype observed in this study was fast acetylator.

The prevalence of the NAT2 phenotype differs geographically, such as standard slow acetylator status in Egypt (83%) and in the United States (67%) but rare in northern Asia (12% in China). Study from Singh in Indian population notified that the dominant phenotype was slow acetylator (55%). Susilowati, et al. reported that in the Malay tribe the dominant phenotype was fast acetylator (62%).[15,16] Pramono,

et al. in the East Nusa Tenggara population also expressed that fast acetylator was the dominant phenotype.[20] A meta-analysis conducted by Paspinodya, et al. stated that fast acetylators were more likely to experience microbiological conversion failure and relapse than slow acetylators. The study also concluded that individual doses for TB might be more effective than standard doses in the DOTS program. This study could not prove this hypothesis because it did not correlate with treatment outcome.[21]

Mutations in the NAT2 gene are responsible for most of the acetylator phenotype affecting plasma concentrations of isoniazid and its metabolites.[12,22] The 1973 WHO report stated the importance of determining the patient's acetylation phenotype in INH administration because NAT transforms the drug in the liver.[8] Variations in the NAT2 gene among different populations might influence INH metabolism, disposition, and side effects. The division of INH acetylation into fast, intermediate, and slow acetylators, shows different plasma drug concentrations after administration of the same dose. The rate of INH elimination also differs between fast and slow acetylators.[6] Patients with the NAT2*4/NAT2*4 genotype (fast acetylator phenotype) exhibited lower INH concentrations than other NAT2 genotypes. Patients with a slow acetylator phenotype have two to seven-fold higher INH concentrations at 3 and 6 hours after drug administration than those with fast acetylator phenotype.[8]

Assessment of plasma INH concentrations is carried out by the chromatographic method, which is faster than other methods.[23] This method is useful for scientific purposes and for keeping track of TB patients undergoing treatment by monitoring changes in drug concentrations. In this study, the median plasma concentration of the drug was obtained after 2 hours of administration, based on the type of acetylator. The median plasma INH concentration for two hours after administration of the drug in rapid acetylators was 1.25 µg/ml (range 0–8.50 µg/ml), lower than that of intermediate acetylators (2.16 µg/ml, range 0–4.33 µg/ml) and slow acetylators (5.24 µg/ml, range 0.25–14.16 µg/ml). The concentrations in this study were lower than that of Kumar, et al., namely 4.1 µg/ml in fast acetylator, 8.1 µg/ml in intermediate acetylator, and 10.2 µg/ml in slow acetylator.[9] Another study by Singh, et al. found the value of INH concentration after 2 hours in fast acetylator was 2.4 µg/ml, while in slow acetylator was 5.6 µg/ml; these results were not much different from the results in this study.[7] The acetylator phenotype was almost the same, namelythe plasma INH concentration in the fast acetylator group was lower than that in the intermediate and slow acetylator groups.

This study analyzed the correlation between plasma isoniazid levels and the distribution of acetylator phenotypes. In both the trimodal and bimodal distributions, no correlations were found. This was in contrast to Kumar, et al., who obtained a significant difference in plasma INH concentrations between the three acetylators.[9] This might be due to the smaller number of samples in this study.

Several studies to date have reported the effect of NAT2 genotype and plasma INH concentration on the clinical condition of patients.[23,24] Adverse effects such as INH-induced hepatotoxicity have been reported from various studies. Based on this, the difference in INH concentration variations based on the NAT2 genotype is essential to know. Slow acetylators with higher INH concentrations are more susceptible to INH-induced hepatotoxicity. A meta-analysis by Wang, et al., 17 of 14 studies consisting of 474 cases and 1446 controls, showed a significant association between NAT2 slow acetylators and the risk of TB drug-induced liver toxicity.[22]

In contrast to slow acetylators, fast acetylators are associated with an increase in the acetylating capacity of the NAT2 enzyme, thereby lowering drug levels and showing poor drug efficacy in some reports. This leads to possibly slower bacteriological conversion rate, resulting in treatment failure, higher risk of recurrence and drug resistance.[21] Many factors affect the efficacy of INH. In addition to plasma INH concentration, the effectiveness of INH is also influenced by the MIC of mycobacterium

tuberculosis in individuals. In patients with low INH concentrations, the drug efficacy in these patients was not necessarily low.[25] In this study and most studies in several regions in Indonesia, the dominant acetylator was fast acetylator. Cases of relapsed TB and MDR TB in Indonesia were quite high based on 2014 WHO data of as many as 7,840 points, and in West Sumatra, the figures were relatively high. However, this study could not conclude the study hypothesis because it did not include data on the outcome of MDR TB patients.

The results of this study supported the importance of knowing the variation of the patient's acetylator phenotype because it was one of the factors which played a role in plasma INH concentrations. Based on this, the INH dosing regimen could be tailored to the individual to increase efficiency and reduce INH side effects and the risk of recurrence and resistance. In addition, this study supported the monitoring of treatment adherence by assessing plasma INH concentrations. In this study, low plasma INH concentration was found, even though the patient was taking medication before the sample was taken. Researchers could only confirm that the patient took the drug on that day. The low INH concentration in these patients could not be ascertained whether it was influenced purely by the acetylator phenotype or other factors such as non-adherence and other host factors.

This study had limitations in the relatively small number of samples, namely from 26 subjects whose venous blood was taken; only 16 patients could be sequenced.

CONCLUSION

The NAT2 genotype polymorphism influenced the acetylation status. The concentration of isoniazid was different in the three groups of fast, intermediate, and slow acetylators. This study found no correlations between the NAT2 acetylator phenotype and plasma INH concentrations among the trimodal and bimodal distributions.

REFERENCES

1. World Health Organization. Global tuberculosis report 2018. World Health Organization. Geneva; 2018.
2. World Health Organization. Global tuberculosis report 2017. World Health Organization. Geneva; 2017.
3. World Health Organization. Global tuberculosis report 2016. World Health Organization. Geneva; 2016.
4. Kementerian Kesehatan Republik Indonesia. Petunjuk teknis pengobatan pasien TB resisten obat dengan paduan standar jangka pendek di fasyankes TB resisten obat. 2017.
5. World Health Organization. WHO Treatment Guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. World Health Organization. Geneva; 2018.
6. Klein DJ, Boukouvala S, McDonagh EM, Shuldiner SR, Laurieri N, Thorn CF, et al. PharmGKB summary: isoniazid pathway, pharmacokinetics. Pharmacogenet Genomics. 2016;26(9):436–44.
7. Singh N, Dubey S, Chinnaraj S, Golani A, Maitra A. Study of NAT2 gene polymorphisms in an Indian population: association with plasma isoniazid concentration in a cohort of tuberculosis patients. Mol Diagn Ther. 2009;13(1):49–58.
8. Zabost A, Brzezińska S, Kozińska M, Błachnio M, Jagodziński J, Zwolska Z, et al. Correlation of N-acetyltransferase 2 genotype with isoniazid acetylation in Polish tuberculosis patients. Biomed Res Int. 2013;2013:853602.
9. Hemanth Kumar AK, Ramesh K, Kannan T, Sudha V, Haribabu H, Lavanya J, et al. N-acetyltransferase gene polymorphisms & plasma isoniazid concentrations in patients with tuberculosis. Indian J Med Res. 2017;145(1):118–23.
10. Pradipta J, Soepandi PZ, Burhan E, Isbaniah F, Agustin H, Handayani D, et al. Adverse Reactions Among Patients Being Treated with

Shorter Multi-Drug Resistant Tuberculosis Regimen at Persahabatan Hospital, Indonesia. Respirology. 2018;23:72–3.

11. Rychlik-Sych M, Skretkowicz J, Gawrońska-Szklarz B, Górnik W, Sysa-Jedrzejowska A, Skretkowicz-Szarmach K. Acetylation genotype and phenotype in patients with systemic lupus erythematosus. Pharmacol Rep. 2006;58(1):22–9.
12. Tanigawara Y, Kita T, Aoyama N, Gobara M, Komada F, Sakai T, et al. N-acetyltransferase 2 genotype-related sulfapyridine acetylation and its adverse events. Biol Pharm Bull. 2002;25(8):1058–62.
13. The Arylamine N-Acetyltransferase Gene Nomenclature Committee. Supplementary Table 2: Distribution and annotation of NAT genes in sequenced genomes of protists (a) [Internet]. The Arylamine N-Acetyltransferase Gene Nomenclature Committee. 2016 [cited 2020 May 1]. Available from: http://nat.mbg.duth.gr/Human NAT2 alleles_2013.htm
14. Magalon H, Patin E, Austerlitz F, Hegay T, Aldashev A, Quintana-Murci L, et al. Population genetic diversity of the NAT2 gene supports a role of acetylation in human adaptation to farming in Central Asia. Eur J Hum Genet. 2008;16(2):243–51.
15. Yuliwulandari R, Sachrowardi Q, Nishida N, Takasu M, Batubara L, Susmiarsih TP, et al. Polymorphisms of promoter and coding regions of the arylamine N-acetyltransferase 2 (NAT2) gene in the Indonesian population: proposal for a new nomenclature. J Hum Genet. 2008;53(3):201–9.
16. Susilowati RW, Prayuni K, Razari I, Bahri S, Yuliwulandari R. High frequency of NAT2 slow acetylator alleles in the Malay population of Indonesia: an awareness to the anti-tuberculosis drug induced liver injury and cancer. Med J Indones. 2017;26(1):7–13.
17. Patin E, Harmant C, Kidd KK, Kidd J, Froment A, Mehdi SQ, et al. Sub-Saharan African coding sequence variation and haplotype diversity at the NAT2 gene. Hum Mutat. 2006;27(7):720.
18. Ensembl. Ensembl genome browser 105 [Internet]. Ensembl. 2020 [cited 2020 Apr 30]. Available from: http://asia.ensembl.org/index.html
19. Sabbagh A, Darlu P, Crouau-Roy B, Poloni ES. Arylamine N-acetyltransferase 2 (NAT2) genetic diversity and traditional subsistence: a worldwide population survey. PLoS One. 2011;6(4):e18507.
20. Pramono AA, Penggoam S, Sahiratmadja E, Utami NV, Achmad TH, Panigoro R. Status Asetilator Gen NAT2 pada Pasien Tuberkulosis dan Tuberkulosis dengan Diabetes Melitus di Kupang, Nusa Tenggara Timur. Maj Kedokt Bandung. 2017;49(1):61–6.
21. Pasipanodya JG, Srivastava S, Gumbo T. Meta-analysis of clinical studies supports the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy. Clin Infect Dis. 2012;55(2):169–77.
22. Wang P, Pradhan K, Zhong X-B, Ma X. Isoniazid metabolism and hepatotoxicity. Acta Pharm Sin B. 2016;6(5):384–92.
23. Chen B, Li J-H, Xu Y-M, Wang J, Cao X-M. The influence of NAT2 genotypes on the plasma concentration of isoniazid and acetylisoniazid in Chinese pulmonary tuberculosis patients. Clin Chim Acta. 2006;365(1–2):104–8.
24. Ellard GA. Variations between individuals and populations in the acetylation of isoniazid and its significance for the treatment of pulmonary tuberculosis. Clin Pharmacol Ther. 1976;19(5 Pt 2):610–25.
25. World Health Organization. Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2018.

Impact of Pulmonary Rehabilitation on Hospitalization Duration, IL-6 Levels, and Respiratory Muscle Power in Hospitalized Community-Acquired Pneumonia Patients

Santony, Iin Noor Chozin, Teguh Rahayu Sartono, Rahmad, Harun Al Rasyid

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya, Dr. Saiful Anwar Hospital, Malang

Abstract

Background: *Pneumonia is acute inflammation of the lung parenchyma. The long duration of hospitalization is associated with increased morbidity, nosocomial infections and treatment costs.*

Methods: *The study was conducted from May to November 2019 at Saiful Anwar Hospital, Malang, with 40 pneumonia patients in the non-intensive community inpatient room divided into 2 groups. The treatment group performed pulmonary rehabilitation measures consisting of breathing exercise, effective coughing techniques, clapping, postural drainage and respiratory muscle training using spirometry incentives.*

Results: *The duration of hospitalization for the treatment group was 2.25 days shorter (p<0.001). The average IL-6 level in the 5th day of the treatment group was lower than without treatment, that was 54.43 pg/ml (p=0.221). The mean of pressure threshold loading in the group without treatment was 31.5 cmH_2O on first day and 36.35 cmH_2O on the 5th day (p <0.001) and on first day treatment group was 32.9 cmH_2O and 39.35 cmH_2O on the 5th day (p=0.001), and the mean value of the 5th day of the treatment group was higher than without treatment (P = 0.015). the mean of the 5th day of the treatment group was higher than without treatment (p=0.06).*

Conclusion: *Pulmonary rehabilitation as adjunctive therapy shortens the duration of hospitalization. In both groups there was a decrease in IL-6 levels on the 5th day compared to zero and the lower IL-6 levels were not significant in the treatment group. There was a significant increase in the value of pressure threshold loading inspiration and expiration day five compared to day zero in the two groups and there was a significant increase in the Pressure Threshold Loading Inspiration mean treatment group compared to no treatment on the 5th day, but the Pressure Threshold Loading Expiration rate showed no significant increase.* ***(J Respirol Indones 2022; 42(1): 34–42)***

Keywords: *Chest physiotherapy; Community pneumonia; Duration of hospitalization; Interleukin-6*

Pengaruh Rehabilitasi Paru terhadap Durasi Rawat Inap, Kadar IL-6, Kekuatan Otot Respirasi pada Pasien Pneumonia Komunitas Rawat Inap

Abstrak

Latar belakang: *Pneumonia adalah peradangan akut pada parenkim paru. Durasi rawat inap yang lama berhubungan dengan meningkatnya angka morbiditas, infeksi nosokomial serta biaya perawatan.*

Metode: *Penelitian dilakukan dari Mei sampai November 2019 di RSUD Dr. Saiful Anwar, Malang, dengan 40 pasien pneumonia komunitas rawat inap ruang non intensif dibagi menjadi 2 grup. Pada grup perlakuan dilakukan tindakan rehabilitasi paru yang terdiri dari breathing exercise, teknik batuk efektif, clapping, postural drainage serta latihan otot pernafasan dengan alat insentif spirometry.*

Hasil: *Durasi rawat inap grup perlakuan lebih pendek 2,25 hari (P<0,001). Rerata kadar IL-6 hari ke5 grup perlakuan lebih rendah dibanding tanpa perlakuan yaitu 54,43 pg/ml(p=0.221). Rerata inspirasi pressure threshold loading grup tanpa perlakuan hari nol adalah 31,5 cmH_2O dan 36,35 cmH_2O pada hari ke-5 (p<0.001) dan grup perlakuan hari nol adalah 32,9 cmH_2O dan 39,35 cmH_2O pada hari ke-5 (p=0.001), serta nilai rerata hari ke-5 grup perlakuan lebih tinggi dibandingkan tanpa perlakuan (P=0,015).Rerata ekspirasi pressure threshold loading grup tanpa perlakuan hari nol adalah 16,3 cmH2O dan 18,75 cmH2O pada hari ke-5 (p=0.001) dan pada grup perlakuan hari nol adalah 18,3 cmH_2O dan 20,0 cmH_2O pada hari ke-5 (p=0.004), Rerata hari ke-5 grup perlakuan lebih tinggi dibandingkan tanpa perlakuan (P=0,06).*

Kesimpulan: *Rehabilitasi paru sebagai terapi penunjang memperpendek durasi rawat inap. Pada kedua grup terdapat penurunan kadar IL-6 pada hari ke-5 dibandingkan hari nol serta kadar IL-6 yang lebih rendah tidak bermakna pada grup perlakuan. Terdapat peningkatan bermakna nilai rerata Inspirasi dan Ekspirasi Pressure Threshold Loading hari ke-5 dibandingkan hari nol pada kedua grup dan terdapat peningkatan bermakna rerata Inspirasi Pressure Threshold Loading grup perlakuan dibandingkan tanpa perlakuan pada hari ke-5, namun rerata Ekspirasi Pressure Threshold Loading didapatkan peningkatan tidak bermakna signifikan.* ***(J Respirol Indones 2022; 42(1): 34–42)***

Kata kunci: *Chest physiotherapy; Pneumonia komunitas; Durasi rawat inap; Interleukin-6*

Correspondence: Santony
Email: santonyliau@ymail.com

INTRODUCTION

Lower respiratory tract infections, including pneumonia, are third among the top 30 causes of mortality worldwide. The World Health Organization (WHO) estimates that pneumonia kills 1.6 million people each year, primarily children and the elderly. Pneumonia is the eighth leading cause of mortality in the United States and the most prevalent cause of death from infectious diseases among patients of all ages. In developed countries such as the United States, the incidence of pneumonia is 12 cases per 1,000 persons, with a 15% mortality rate.[1]

Pneumonia and influenza are the sixth and seventh leading causes of mortality in Indonesia, according to the South East Asian Medical Information Center (SEAMIC) Health Statistics. Pneumonia is one of the top ten hospitalized diseases in Indonesia, with a crude fatality rate (CFR) of 7.6%, the highest when compared to other diseases.[2]

Interleukin-6 (IL-6) is a pleiotropic cytokine with broad biological activity in immune regulation, hematopoiesis, inflammation, and oncogenesis. The selection of IL-6 among other inflammatory cytokines is based on its rapid development, detection from plasma when inflammatory stimuli appear, and the availability of examination kits. It can be easily detected compared to other cytokines.[3] Interleukin-6 is important because it may be identified during the early host response to infection and can stimulate the migration of activated T cells in vitro.[4] Therefore, this study was carried out to investigate the levels of IL-6 in community-acquired pneumonia (CAP) patients admitted to a non-intensive ward at Saiful Anwar Hospital in Malang.

Pulmonary rehabilitation is a group of treatments designed to increase respiratory efficiency, increase lung expansion, strengthen the respiratory muscles, and remove secretions from the respiratory system. Pneumonia patients have increased sputum production, and it is difficult to expel. This means that pulmonary rehabilitation can be used as an additional therapy for pneumonia patients. However, some literature still says that there is no significant benefit when pulmonary rehabilitation is given to pneumonia patients. The purpose of pulmonary rehabilitation is not only to help expel secretions but also to increase the strength of the respiratory muscles, which consist of the muscles of inspiration and expiration. The value of inspiratory and expiratory muscle strength can be assessed by inspiratory and expiratory pressure threshold loading.

Until now, no research has been carried out on pulmonary rehabilitation associated with length of stay, IL-6 levels, and respiratory muscle strength in community pneumonia patients hospitalized in a non-intensive room at Saiful Anwar Malang Hospital. Therefore, researchers are interested in conducting this research. In addition, researchers consider that pulmonary rehabilitation is essential in managing non-intensive ward inpatient community pneumonia patients to save costs.

METHOD

This research was conducted by the experimental method pre-post-test control group design in community-acquired pneumonia (CAP) patients hospitalized in non-intensive wards at Dr. Saiful Anwar Hospital, Malang in June-November 2019. Samples were obtained by consecutive sampling with simple random sampling on pneumonia patients in non-intensive wards which met the inclusion and exclusion criteria. Patients between the ages of 18 and 65 who were willing to participate and gave informed consent were eligible for this research. Patients with HIV/AIDS, patients with acute or chronic cerebrovascular illness, patients with contraindications for pulmonary rehabilitation, pneumonia patients who have proved to be resistant to empiric treatment, pulmonary TB patients, and patients with ongoing hemoptysis or a history of hemoptysis in the last 3 months were excluded in the research.

The sampling of this research was carried out in the emergency room and the non-intensive inpatient wards of Saiful Anwar Hospital, Malang, with the consent of the patient and the patient's family, who signed the informed consent in the consultation

room located in each ward. Forty CAP patients who met the inclusion and exclusion criteria and were willing to participate in the study were divided into 2 groups: the control and the treatment group. Patients in the treatment group will get pulmonary rehabilitation from the physical medicine and rehabilitation department staff at Saiful Anwar Hospital in Malang, which will include chest physiotherapy methods like as clapping, coughing, deep breathing techniques, postural drainage, and inspiratory muscle training. On day zero and day five, both groups' IL-6 levels and the value of their inspiratory and expiratory pressure threshold loading will be assessed. The paired T-test will be used to determine the effect of pulmonary rehabilitation on IL-6 levels and inspiratory and expiratory pressure threshold loading values. Meanwhile, the Mann Whitney test will be used to measure the effect of pulmonary rehabilitation on the length of hospitalization of patients.

Processing and data analysis using IBM SPSS software version 24.0. The research data are presented in the form of mean +/- SD. Then the normality test was carried out with the Shapiro-Wilk test and the Kolmogorov-Smirnov test. If the normality of the data is met ($P \geq 0.05$), proceed with the independent parametric T-test. If the normality of the data is not met, then a non-parametric test with the Mann Whitney test is performed. Statistical tests were carried out with the SPSS 24 program with 95% confidence level, alpha = 0.05.

RESULTS

In this study, the average duration of hospitalization for patients in the control group was 7.60 days, with the most extended treatment period being 10 days and the shortest treatment period being 5 days. Patients who received pulmonary rehabilitation therapy had a shorter hospitalization period, with an average of 5.35 days. The most extended hospitalization period was 7 days, and the shortest hospitalization period was 4 days. There is a difference in the hospitalization period of 2.25 days. In the Mann Whitney test, the difference in hospitalization was statistically significant ($P<0.001$).

Table 1. Analysis of the duration of hospitalization in the treatment and control groups

Duration of Hospitalization	Control	Treatment
Mean (+/-SD)	7.6±1.53 days	5.35±0.671 days
Median (+/- IQR)	8±2 days	5±1 days
Mann Whitney Test Results	$P<0.001$	

The level of IL-6 in the controlgroup on day zero was 67.76 pg/ml and after being given standard therapy (antibiotics) on day five was 54.43 pg/ml. There was a decrease in IL-6 level on day zero compared to day five in the control group. However, the Wilcoxon test revealed that there was no statistically significant change in IL-6 levels on day zero versus day five ($P=0.502$).

The level of IL-6 in the group that received treatment on day zero was 36.27 pg/ml, while the level after five days of rehabilitation was 34.36 pg/ml. The levels of IL-6 of the treatment group decreased on day five, however the Wilcoxon test revealed no significant difference between IL-6 levels on day zero and day five ($P=0.628$).

On the fifth day, the treatment group's IL-6 level was 34.56 pg/ml, whereas the control group's level was 54.43 pg/ml. As a result, the levels of IL-6 on day five were lower in the treatment group than in the control group. The Mann Whitney test, however, revealed no significant change in IL-6 levels on day five between the control and treatment groups ($P=0.221$).

Table 2. Analysis of IL-6 Levels on Day Zero and Day Five in the Treatment and Control Groups

IL-6 Levels	Treatment	Control
Day Zero		
Mean (+/- SD)	36.27±60.14 pg/ml	67.76±79.01 pg/ml
Median (+/-IQR)	9.96±51.88 pg/ml	39.21±107.49pg/ml
Day five		
Mean (+/- SD)	34.36±69.4pg/ml	54.43±76.74 pg/ml
Median (+/-IQR)	6.38±29.13 pg/ml	22.75±68.05 pg/ml
Wilcoxon Test Results	$P=0.628$	$P=0.502$
Mann Whitney Test Results	Day five $P= 0.221$	

Because the difference in IL-6 days zero between the control and treatment groups was discovered to be highly substantial in the study data, a separate test was performed to assess whether the difference was statistically significant. On day zero,

the average IL-6 level in the treatment group was 36.27±60.14 pg/ml, while it was 67.74±79.01 pg/ml in the control group. The Mann Whitney test, with *P*=0.086, indicates that there is no significant difference in IL-6 levels on day zero between the treatment and control groups.

The average inspiratory pressure threshold loading (IPTL) value in the day zero treatment group was 31.5 cmH_2O and increased to 36.35 cmH_2O on the 5th day of conventional therapy. Therefore, through the Wilcoxon test, *P*<0.001, it can be concluded that conventional therapy (antibiotic therapy) significantly increases the value of IPTL.

In the treatment group, the IPTL average value on day zero was 32.9 cmH_2O. This value increased after giving pulmonary rehabilitation for 5 days to 39.35 cmH_2O. The Wilcoxon test (*P*=0.001) shows that further pulmonary rehabilitation therapy can considerably raise the value of the IPTL.

Table 3. Analysis of IPTL Value on Day Zero and day five of the Treatment and control Groups

Threshold Loading Inspiration	Treatment	Control
Day Zero		
Mean (+/- SD)	32.9 ±8.81 cmH_2O	31.50±4.39 cmH_2O
Median (+/-IQR)	35.5±15.5 cmH_2O	31 ± 8.5 cmH_2O
Day five		
Mean (+/- SD)	39.35±3.29cmH_2O	36.35± 5,18 cmH_2O
Median (+/-IQR)	41 ± 2.25 cmH_2O	38.5 ± 11 cmH_2O
Wilcoxon Test Results	*P*=0.001	*P*<0.001
Mann Whitney Test Results	Day five: *P*=0.015	

On day five, the treatment group's average inspiratory pressure threshold loading was 39.35 cmH_2O, which was greater than the control group's value of 36.35 cmH_2O. As a result, while the Mann-Whitney test yielded a significant value of *P*=0.015, it can be inferred that following adjunctive therapy, there was an increase in the average pressure threshold loading value of 3.15 cmH_2O compared to the control group.

The average expiratory pressure threshold loading in the control group was 16.3 cmH_2O on day zero and climbed to 18.75 cmH_2O on day five. As a result of the Wilcoxon test (*P*=0.001), conventional treatment can significantly boost the expiratory pressure threshold loading value.

On day zero, the average expiratory pressure threshold loading in the treatment group with pulmonary rehabilitation as supplementary therapy was 18.3 cmH_2O. On the fifth day, this number climbed to 20.0 cmH_2O. According to the Wilcoxon test (*P*=0.004), administering pulmonary rehabilitation treatment can significantly increase the average expiratory pressure threshold load value.

Table 4. Analysis of the IPTL Expiration Value on Day Zero and Day Five of the Treatment and Control Groups

Threshold Loading Ekspiration	Treatment	Control
Day Zero		
Mean (+/- SD)	18.3±2.17 cmH_2O	16.3±3.59 cmH_2O
Median (+/-IQR)	19 ± 3.5 cmH_2O	18 ± 6.5 cmH_2O
Day five		
Mean (+/- SD)	20 ± 0 cmH_2O	18.75±1.91 cmH_2O
Median (+/-IQR)	20 ± 0 cmH_2O	20 ± 3 cmH_2O
Wilcoxon Test Results	*P*=0.004	*P*=0.001
Mann Whitney Test Results	Day five: *P*= 0.06	

On day five, the treatment group's average expiratory pressure threshold loading was 20.0 cmH2O, which was greater than the control group's value of 18.75 cmH_2O. The Mann Whitney test, however, revealed that the results were not statistically significant (*P*=0.06). Nonetheless, on day five, the treatment group had a greater average expiratory pressure threshold loading than the control group, albeit this difference was not statistically significant.

DISCUSSION

In this study, the average hospitalization period for patients receiving standard therapy was 7.60 days, with the most extended treatment period being ten days and the shortest treatment period being five days. Patients who received standard treatment plus pulmonary rehabilitation had a shorter hospitalization period, with an average of 5.35 days. The most extended hospitalization period was seven days, and the shortest hospitalization period was four days. There is a difference in the hospitalization period of 2.25 days. This is consistent with a study conducted by Yang et al. who showed that chest physiotherapy (osteopathic manipulative) reduced the length of hospital stay by 2.0 days (mean difference (MD): 2.0

days, 95% CI = -3.5 to -0.6) and 1.4 days (MD: 1.4 days, 95% CI = -2.8 to -0.0).[5]

This study also had similar results to those of Carratalà et al., who stated that three steps of physiotherapy reduced the duration of hospitalization by two days in pneumonia compared to standard conventional therapy and had significant economic implications.[6]

However, the results of this study were different from those of Jose and Corso, who stated that there was no difference between the treatment and control groups in lung function, C-reactive protein (CRP), or length of hospital stay.[7]

In this study, pulmonary rehabilitation consisted of two main components: chest physiotherapy and respiratory muscle training. Chest physiotherapy consists of effective coughing techniques, deep breathing techniques, clapping and postural drainage. The goal of chest physiotherapy is to improve the patient's respiratory status and accelerate recovery by increasing airway clearance in lung disease associated with hypersecretion and reducing airway resistance. Chest physiotherapy is best used for patients with excessive secretions (more than 30 ml/day) and poor coughing ability. Chest physiotherapy used as an adjunctive treatment in primary pneumonia is useful for assisting clearance of inflammatory exudate in patients whose airways or lung parenchyma are pathologically affected by microbial infection.

Respiratory muscle strength training (RMST) focuses on increasing inspiratory and expiratory muscle capacity. The mainly trained muscles are the muscles that help with breathing, namely the inspiratory muscles consisting of the diaphragm and the external intercostals as the primary muscles and the sternocleidomastoid as the auxiliary muscles. The forces for expiration consist of the internal intercostals and abdominal muscles such as the rectus transversus and obliques. Respiratory muscle strength training will increase the strength and endurance of the diaphragm muscle and reduce lung hyperinflation, thereby reducing shortness of breath. The two main components of the exercise described above will improve the clinical condition of pneumonia patients and accelerate the length of their hospitalization.

This study showed that the average value of IL-6 levels on day five of the treatment and control groups was lower than on day zero. This is consistent with the theoretical hypothesis that IL-6 levels decrease with improvement in pneumonia. This study was based on the results of research by Bacci et al. that showed a significant decrease in IL-6 levels on day one and day seven, where the median value of IL-6 decreased from 24 pg/ml to 8 pg/ml with P= 0.016.[8]

On the 5th day of the treatment group, the level of IL-6 was 34.56 pg/mL, while in the control group it was 54.43. It can be concluded that the levels of IL-6 on day five were lower in the treatment group than in the control group. This indicates that CAP patients in the treatment group had faster clinical improvement than those without treatment. The levels of IL-6 on day five were lower in the treatment group, although not statistically significant (P>0.05). From the research of Andrijevic et al., hospitalized community pneumonia patients with elevated IL-6 had a 93.4% higher risk of higher mortality. A cut-off value of 20.2 pg/ml IL-6 showed a sensitivity of 84% and a specificity of 87% for predicting mortality. In this study, there was an improvement in pneumonia and a decrease in IL-6 levels on day five.[9]

In the research of Martin et al., it was found that high levels of IL-6 had a high predictive value for the early and late failure of therapy on day one and for the late loss of treatment on day three, suggesting that IL-6 was a good marker for progression to treatment failure. This is because of this study, which showed that in the treatment group, there were low levels of IL-6 on day five, which was followed by the improvement of pneumonia patients' treatment success.[10]

Interleukin-6 plays an essential role during the transition between innate and acquired immunity. Acute inflammation begins with infiltration by neutrophils, which are then replaced by monocytes and T cells after 24–48 hours to prevent tissue damage due to accumulation of proteases (secreted by neutrophils) and ROS (Reactive Oxygen Species)

at the site of inflammation. Endothelial cells and other vascular elements activated by microbes, together with IL-1, TNF, and IL-6, produce various chemokines. Interleukin-6 also induces neutrophil apoptosis, thereby resolving acute neutrophil infiltration.

An immunological response develops in pneumonia. When Toll-like receptors (TLR2, TLR1, and TLR6) attach to pathogenic molecules that are phagocytized, they activate the Nucleotide-binding Oligomerization Domain (NOD) signal, which initiates the body's immune system via NF-Kβ. Macrophages that phagocytize infections will create surface proteins from these microorganisms at the Major Histocompatibility Complex binding site (MHC). These MHCs will then express proteins that attract particular T cells, which will aid in the activation of cytokines and suitable antibodies. PRR activation results in the production of pro-inflammatory molecules like as TNF-α, IL-1β, IL-2, IL-6, IL-8, and IFN-γ, as well as anti-inflammatory cytokines that stimulate both cellular and reversal responses.[11,12]

Because of the inflammation caused by microorganism infection, IL-6 levels will rise in the first 6 hours of pneumonia. After the improvement in pneumonia, IL-6 levels will decrease, which corresponds to a shorter hospitalization period in the group without treatment (standard therapy (antibiotics) plus, pulmonary rehabilitation). In this study, the levels of IL-6 on the fifth day were lower in both groups than on the first, which corresponded to the improvement in pneumonia following therapy. On the fifth day, the treatment group's IL-6 levels were lower than the control group's.

The baseline values for IL-6 levels in the two groups were different. The treatment group had lower IL-6 levels than the control group. This was due to the fact that the treatment group had a lower average PSI value than the control, and the PSI value represented the severity of the pneumonia. As a result, the amount of IL-6, a biomarker for inflammation, is very certainly connected to the severity of pneumonia. The difference in IL-6 levels at zero days between the both groups, however, was not statistically significant, suggesting that the baseline results for differing IL-6 levels might be related to the overall standard variation across patients.

The goal of respiratory muscle strength training (RMST) is to increase inspiratory and expiratory muscular capacity. RMST improves diaphragm muscle strength and endurance while decreasing lung hyperinflation and shortness of breath. This training also enhances the usage of respiratory muscle savings, lowering oxygen consumption and enhancing exercise tolerance.

According to the findings of this study, the average value of inspiratory pressure threshold load increased considerably on day five compared to day zero in both the treatment and control groups, with the treatment group having a higher average value on day five than the control group. Similarly, the average value of the expiratory pressure threshold loading rose on day five compared to day zero in both the treatment and control groups. On the fifth day, the average value of the expiratory pressure threshold loading in the treatment group was greater than in the control group. These findings point to an increase in the strength of both the inspiratory and expiratory muscles.

This is in accordance with the research of Enright et al. who found that after training there was a significant increase in Pimax and SPimax ($p<0.05$), TDIcont ($P<0.05$), TR ($P<0.05$), vital capacity ($P<0.05$), TLC ($P<0.05$), and PWC ($P<0.05$), and reductions in anxiety scores ($P<0.05$) and depression scores ($P<0.01$) were noted in group 1 patients compared to group 3 patients. Only group 3 patients showed significantly improved Pimax and SPimax (both $P<0.05$). There was no statistically significant difference between the groups of patients. An 8-week program of high-intensity inspiratory muscle training (IMT) produced considerable advantages for CF patients, including increased IMF and diaphragmatic thickness (during contraction), increased lung capacity, enhanced PWC, and improved psychosocial status.[13]

In the study of Ramirez et al., where the aim of this study was to evaluate the effect of a specific inspiratory muscle training protocol on inspiratory muscle structure in patients with chronic obstructive

pulmonary disease. Fourteen patients (male, FEV_1, 24±7% predicted) were randomized to inspiratory or sham muscle groups. Breathing was monitored using a respiratory device threshold for 30 minutes per day, five times a week, for 5 consecutive weeks. The inspiratory training group was subjected to an inspiratory load equivalent to 40 to 50% of their maximal inspiratory pressure. Biopsies of the external intercostal muscles and the vastus lateralis (control muscle) were taken before and after the training. Muscle samples were processed for morphometric analysis using monoclonal antibodies against myosin I and II heavy chain isoforms. An increase in inspiratory muscle strength and endurance was observed in the inspiratory training group. This increase was associated with an increase in the proportion of type I fibres (about 38%, $P<0.05$) and in the size of type II fibres (about 21%, $P<0.05$) in the external intercostal muscles. No changes were observed in the control muscles. This study demonstrates that inspiratory training causes particular functional enhancement of inspiratory muscles as well as adaptive changes in the anatomy of the external intercostal muscles.[14]

The EPT value in the control group on the fifth day compared to day zero increased significantly ($P<0.05$), while in the control group and the comparison of the EPT value on the fifth day, the two groups got an increased but not significant value ($P>0.05$). This is because the upper limit of the maximum EPT measurement is 20 cmH_2O, in some patients, an EPT value of 20 cmH_2O has been obtained from day zero.

In this study, the duration of muscle training inspiration was five days with two sets of exercises in the morning and two sets of activities in the afternoon, with a daily minimum of ten minutes. According to the literature, it is recommended that the duration of activity be thirty minutes per day, which is divided into one to two training sessions with a minimum duration of three to five minutes. It is recommended that exercise be done every day. Functional improvement and adaptive structural changes can occur after five weeks of training. Most of the training benefits will disappear after six months without exercise.[15]

The study by Ramirez et al. found that inspiratory muscle training was associated with structural changes in the muscles, as assessed by the fibre type and fibre size distribution. In particular, the proportions of type I fibre ($P<0.05$) and type II fibre size ($P<0.05$) increased after training. This study aimed to evaluate structural changes in the respiratory muscles of patients with COPD after a specific respiratory muscle training program. Significant increases were observed in the proportion of type I fibres (about 38%) and the size of type II fibres (about 21%) of the external intercostal muscles after the training period. These findings suggest that the superficial intercostal muscles of patients with severe COPD can express structural remodeling. The functional improvement caused by inspiratory muscle training (in terms of inspiratory muscle strength and endurance) can be partially explained by structural adaptations in the inspiratory muscles.[14]

Several studies have reported that inspiratory muscle strength and endurance can be increased with specific training, while other studies have not found significant changes in inspiratory muscle function.[16,17] Differences in studies of inspiratory training can differ by differences either in duration or in inspiratory muscle loading. Taking this into consideration, targeted inspiratory muscle training has been shown to increase inspiratory muscle function when the intensity is measured and reaches 20% of the PImax.[14]

The research findings of Ramirez et al. highlight three main concepts. First, muscle response; Research shows that the external intercostal muscles of patients with COPD retain the capacity to improve after a short training period. Similar findings were also found in the peripheral muscles of patients with COPD after general muscle training. This response was demonstrated in the inspiratory muscle group of patients with severe airflow obstruction in one study. Second, functional and structural changes; the results allowed us to hypothesize that the increase in muscular endurance and inspiratory muscle strength after specific training could be associated with changes in the isoform of MyHC (as obtained by an increase in MyHC-I-expressing fibres) and an

increase in fibre size (especially in type II fibres). Other factors, such as adaptation to additional inspiratory loading (e.g., decreased dyspnea), learning of specific manoeuvres, or even the placebo effect, may also increase inspiratory muscle strength and endurance. The third is specificity; it was found that inspiratory muscle training had a specific functional and structural impact only on trained muscles. This study included data from unaffected muscles (legs) as a negative control. When the pre- and post-training results were compared, no changes were observed either in fibre size or in the proportion of fibre types of the vastus lateralis (control muscle).

Similarly, effects on other respiratory muscle groups (e.g., changes in expiratory muscle function) were not found. These facts support the conclusion that inspiratory training has only a specific effect on the trained muscles and the hypothesis that structural adaptation occurs only in the inspiratory muscles. However, the study design did not enable us to gain total confidence in the structural changes in the external intercostals representing the inspiratory muscles in general. The diaphragm is the most important of the inspiratory muscles. Still, there are apparent ethical and practical difficulties in repeatedly accessing the diaphragm of healthy subjects or stable patients with COPD, even if a thoracotomy is performed for other reasons (e.g., reduced lung volume). lung, lung cancer, or transplant).[14]

CONCLUSION

Pulmonary rehabilitation can reduce the length of stay for pneumonia patients at Saiful Anwar Hospital in Malang's non-intensive wards. When compared to the control group, pulmonary rehabilitation reduced IL-6 levels on the fifth day. In CAP inpatients, however, it was not statistically significant. Furthermore, there was a drop in IL-6 levels on the fifth day as compared to day zero. Nonetheless, it was not statistically significant in either the treatment or control groups. In both the treatment and control groups, the average value of inspiratory and expiratory pressure threshold loading rose considerably on day five compared to day zero in community pneumonia patients hospitalized in a non-intensive ward at Saiful Anwar Hospital, Malang. On day five, the average value of inspiratory pressure threshold loading was much greater. Nonetheless, the average value of the expiratory pressure threshold loading in the treatment group was negligible (P>0.05) when compared to the control group.

REFERENCES

1. Wibisono MJ, Winariani, Hariadi S. Pneumonia. In: Buku Ajar Ilmu Penyakit Paru. Surabaya: IPP FK. Unair RSUD Dr. Soetomo; 2010. p. 153–74.
2. Perhimpunan Dokter Paru Indonesia. Pneumonia Komunitas: Pedoman Diagnosis dan Penatalaksanaan di Indonesia. Jakarta: Perhimpunan Dokter Paru Indonesia; 2014. 3–35 p.
3. Pallás Beneyto LA, Rodríguez Luis O, Saiz Sánchez C, Coltell O, Bautista Rentero D, Miguel Bayarri V. [Prognostic value of interleukin 6 for death of patients with sepsis]. Med Clin (Barc). 2016;147(7):281–6.
4. Kishimoto T. IL-6: from its discovery to clinical applications. Int Immunol. 2010;22(5):347–52.
5. Yang M, Yan Y, Yin X, Wang BY, Wu T, Liu GJ, et al. Chest physiotherapy for pneumonia in adults. Cochrane database Syst Rev. 2013;(2):CD006338.
6. Carratalà J, Garcia-Vidal C, Ortega L, Fernández-Sabé N, Clemente M, Albero G, et al. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. Arch Intern Med. 2012;172(12):922–8.
7. José A, Dal Corso S. Inpatient rehabilitation improves functional capacity, peripheral muscle strength and quality of life in patients with community-acquired pneumonia: a randomised trial. J Physiother. 2016;62(2):96–102.
8. Bacci MR, Leme RCP, Zing NPC, Murad N, Adami F, Hinnig PF, et al. IL-6 and TNF-α serum

levels are associated with early death in community-acquired pneumonia patients. Brazilian J Med Biol Res = Rev Bras Pesqui medicas e Biol. 2015;48(5):427–32.

9. Andrijevic I, Matijasevic J, Andrijevic L, Kovacevic T, Zaric B. Interleukin-6 and procalcitonin as biomarkers in mortality prediction of hospitalized patients with community acquired pneumonia. Ann Thorac Med. 2014;9(3):162–7.
10. Martin-Loeches I, Valles X, Menendez R, Sibila O, Montull B, Cilloniz C, et al. Predicting treatment failure in patients with community acquired pneumonia: a case-control study. Respir Res. 2014;15(1):75.
11. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a016295.
12. Mat-Nor MB, Md Ralib A, Abdulah NZ, Pickering JW. The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality. J Crit Care. 2016;33:245–51.
13. Enright S, Chatham K, Ionescu AA, Unnithan VB, Shale DJ. Inspiratory muscle training improves lung function and exercise capacity in adults with cystic fibrosis. Chest. 2004;126(2):405–11.
14. Ramírez-Sarmiento A, Orozco-Levi M, Güell R, Barreiro E, Hernandez N, Mota S, et al. Inspiratory muscle training in patients with chronic obstructive pulmonary disease: Structural adaptation and physiologic outcomes. Am J Respir Crit Care Med. 2002;166(11):1491–7.
15. Geddes EL, Reid WD, Brooks D, O'Brien K, Crowe J. A primer on inspiratory muscle trainers. Buyers Guide for the European Respiratory Society. 2006;59–67.
16. Liu W, Mu X, Wang X, Zhang P, Zhao L, Li Q. Effects of comprehensive pulmonary rehabilitation therapy on pulmonary functions and blood gas indexes of patients with severe pneumonia. Exp Ther Med. 2018;16(3):1953–7.
17. Weiner P, Magadle R, Berar-Yanay N, Davidovich A, Weiner M. The cumulative effect of long-acting bronchodilators, exercise, and inspiratory muscle training on the perception of dyspnea in patients with advanced COPD. Chest. 2000;118(3):672–8.

The Effect of Inspiratory Breathing Muscle Exercise Using Respirometer on Changes in Lung Function and Dyspnea Severity in Tuberculosis Pleurisy Patients

Irmaini, Herry Priyanto, Dewi Behtri Yanifitri

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, dr. Zainoel Abidin Banda Aceh Regional Public Hospital, Banda Aceh

Abstract

Background: *Respirometer has been commonly used to improve lung function, prevent atelectasis and respiratory complications after surgery. The effectiveness of respirometer to improve lung re-expansion in pleural effusion has not been well studied. So far there is no such study implemented to examine this association in pleural effusion particularly tuberculosis pleurisy in Aceh.*

Method: *This was an experimental pretest-posttest controlled trial in patients with tuberculosis pleurisy hospitalized in dr. Zainoel Abidin Hospital between July and December 2019. Systematic random sampling was used to gather 40 samples, which then divided into intervention and control group consisted of 20 people in each group. All participants performed spirometry and were assessed for dyspnea severity using Borg scale after thoracocentesis and repeated 6 days later. Only intervention group received exercise using respirometer. Data were examined statistically using paired T-test and Mann Whitney Test.*

Results*: The majority of participants were male (68%) with mean age of 42 years old. Around one-third of samples were smokers with mean Brinkman Index of 273 (moderate). The nutritional status was mostly good with mean BMI of 21 (normal). There were significant improvements of FEV1 and FVC values before and after 6 days in both groups. However, if the improvements were compared between intervention and control groups, only FVC improved significantly in intervention group (*P= *0.019) whereas FEV1 improved in both groups without significant difference (*P= *0.456). Similar result was seen in dyspnea severity where both groups experienced improvement after 6 days with or without intervention.*

Conclusion*: Inspiratory muscle exercise using respirometer could improve lung function, particularly FVC value, significantly and could be an option for additional therapy to help lung re-expansion in tuberculosis pleurisy.* ***(J Respirol Indones 2022; 42(1): 43–51)***

Keywords*: respirometer, lung function, tuberculosis pleurisy, dyspnea*

Pengaruh Latihan Otot Pernapasan Inspirasi Menggunakan Respirometer terhadap Perubahan Fungsi Paru dan Derajat Sesak Napas pada Pasien Pleuritis Tuberkulosis

Abstrak

Latar Belakang*: Respirometer sering digunakan untuk memperbaiki fungsi paru, mencegah atelektasis dan mencegah komplikasi respirasi setelah pembedahan. Efektivitas respirometer dalam membantu pengembangan paru pada efusi pleura masih belum banyak diketahui. Hingga saat ini belum ada penelitian terkait yang dilakukan pada pasien efusi pleura khususnya pleuritis tuberkulosis (TB) di Aceh.*

Metode*: Penelitian ini bersifat eksperimental dengan uji* pretest-posttest *terkontrol pada pasien pleuritis TB yang dirawat di RSUD dr. Zainoel Abidin Banda Aceh periode Juli hingga Desember 2019. Sampel diambil secara acak dan sistematik hingga diperoleh 40 sampel terbagi menjadi 20 orang di kelompok intervensi dan 20 orang kontrol. Semua sampel diperiksa spirometri dan dinilai derajat sesak napas menggunakan skala Borg setelah dilakukan torakosentesis dan diulangi 6 hari kemudian. Hanya kelompok intervensi yang menerima latihan respirometer selama 6 hari. Data diuji menggunakan uji T-berpasangan dan uji* Mann-Whitney.

Hasil*: Mayoritas sampel adalah laki-laki (68%) dengan rerata usia 42 tahun. Sepertiga sampel masih merokok dengan rerata Indeks Brinkman 273 (sedang). Status gizi umumnya baik dengan rerata IMT 21. Nilai VEP1 dan KVP meningkat secara bermakna pada kedua kelompok setelah 6 hari. Akan tetapi apabila dibandingkan antara kelompok intervensi dan kontrol, hanya peningkatan nilai KVP yang bermakna secara statistik (*P= *0,019) sementara peningkatan nilai VEP1 pada kedua kelompok hampir sama (*P= *0,456). Setelah 6 hari, perbaikan sesak napas dijumpai pada kedua kelompok baik dengan atau tanpa latihan respirometer*

Kesimpulan*: Latihan pernapasan otot inspirasi menggunakan respirometer dapat meningkatkan fungsi paru khususnya nilai KVP dan dapat menjadi terapi tambahan untuk membantu pengembangan paru pada pasien pleuritis TB.* ***(J Respirol Indones 2022; 42(1): 43–51)***

Kata kunci: *respirometer, fungsi paru, pleuritis TB, sesak napas*

Corresponding author: Irmaini
Email: irmaini13@gmail.com

INTRODUCTION

Tuberculous pleurisy (TP) is another name for pleural effusion due to tuberculosis infection and is the second most common form of extrapulmonary tuberculosis. Tuberculous pleurisy is the most common cause of pleural effusion in countries with endemic tuberculosis. The prevalence of TP differs in different parts of the world, ranged from about 4% in the United States and Brazil to 20% in North Africa. In Korea, TP is found in 7.3% of TB patients and constitutes of 35% among all extrapulmonary TB.[1] Light stated that 3–25% of TB patients will develop TB pleurisy.[2]

Pleural effusion has a significant influence on the function of the respiratory system. Pleural effusion causes changes in the dynamic balance of lung volumes and chest wall volumes. As a result, there is a ventilation barrier effect, respiratory restriction occurs, the chest wall expands, and the work efficiency of the inspiratory respiratory muscles decreases. Restriction abnormalities in pleural effusion are characterized by decreased vital lung capacity (VLC), functional residual capacity (FRC) and total lung capacity (TLC). Study from Krell and Rodarte showed that lung volume decreased by 1/3 the amount of fluid outflow, and chest volume increased by 2/3 the amount of pleural effusion. Decreased lung volume was primarily due to reduced lower lobe volume with minimal change in upper lobe volume.[3]

Pleural effusion also causes decreased lung compliance and increased chest wall compliance. This dynamic property change can be reversed by deep breathing and lung inflation. Decompression of the lungs and the reopening of several air cavities in the lungs accompanied by a decrease in the surface pressure of the alveoli are important mechanisms which can restore lung function. This situation can be achieved by breathing deeper where more air enters the lungs.[4]

Management of pleural effusion is individualized. The protocol for treating pleural effusions includes administering oxygen therapy and therapy for lung expansion such as thoracentesis and chest physiotherapy.[5,6]

One form of exercise that has been more commonly used is the respirometer, better known as incentive spirometry.[7] Exercise using this respirometer is one of the therapeutic options for pulmonary hyperinflation.[5] This exercise can increase the strength and endurance of the respiratory muscles and improve respiratory complaints such as shortness of breath.[8] The respirometer is designed to improve the performance of the inspiratory muscles, restore or stimulate normal breathing patterns, maintain a patent airway and prevent and correct atelectasis.[9]

Several previous studies had shown the benefits of inspiratory breathing muscle exercises using a respirometer. Valenza, et al. stated that incentive spirometry and mobilization combined with chest drainage and medication in patients with pleural effusion showed significant improvements in vital capacity values, FEV_1 and FVC compared to the control group, they also exhibited better clinical improvement and shorter treatment periods.[7]

Agarwal, et al. in India, also pointed out that incentive spirometry effectively improved lung expansion in patients with pleural effusion.[10] Respirometers were also able to improve lung function and increased exercise capacity when combined with physical exercise. This was asserted by Weiner, et al. as they found a significant increase in lung function in the intervention group, namely an increase in FEV_1 value and an increase in muscle strength in the group that received incentive spirometry after two weeks of exercise.[11]

Although respirometers have been widely used, there has been no study which evaluates how it affects changes in lung function and dyspnea severity in pleural effusion patients treated at RSUD dr. Zainoel Abidin. This study was aimed to examine the correlation of inspiratory muscle exercises using a respirometer and the changes in lung function and also dyspnea severity in patients with TB pleurisy treated at RSUD dr. Zainoel Abidin.

METHOD

This was an experimental study using a pretest-posttest controlled trial design conducted at RSUD dr. Zainoel Abidin Banda Aceh. A systematic random sampling was carried out from July to December 2019. The number of study subjects were 40 patients diagnosed with clinical TB pleurisy by a pulmonary specialist. The sample was divided evenly into 2 groups; 20 subjects in each intervention and control group. Apart from receiving thoracentesis and medication, the intervention group also received inspiratory breathing muscle training using a respirometer for 6 days, while the control group only received thoracentesis and medication.

The inclusion criteria were subjects aged 18 to 65 years old who had a willing to join the study with good general condition, cooperative and able to perform pulmonary function test and exercises using a respirometer. We excluded subjects who hadever received anti-tuberculosis drugs, could not be performed a thoracentesis, had hemoptysis, hydropneumothorax, loculated pleural effusions or recurrent pleural effusions, lung tumours, mediastinal tumours and other lung diseases, cardiomegaly, ascites, history of the eye or thoracoabdominal surgery in the last 6 months and had contraindications for spirometry examination.

The data was obtained in the form of primary data. Data collection and spirometry examination were carried out directly by the researcher. Patients diagnosed with clinical TB pleurisy by a pulmonologist who met the inclusion and exclusion criteria were asked to participate in the study and signed an informed consent. Thoracentesis were performed on the subjects until the pleural fluid production was <100 ml/day.

We did the examination of lung function using a spirometer (Spirolab, all in one Portable Desktop Spirometer for Spirometry test with oximetry option) and measured the dyspnea severity using Borg scale. The data obtained became the baseline data.

Furthermore, the subjects in intervention group were educated about the technique of using a respirometer (Incentive Spirometry Medinet–Italy, a Respiratory Exercise System for Inspiration) 5–6 times daily for 6 days. After six days, a spirometry re-examination and measurements of dyspnea severity were performed in both groups. The data were then tabulated and displayed in mean±standard deviation. The difference between pre- and post-intervention results was analyzed using paired T-test at 95% Confidence Interval and *P* value of 0.05. The Mann-Whitney test was used to compare the mean scores of the two groups at the 95% Confidence Interval and *P*=0.05.

RESULTS

This study divided the study subjects into 2 groups, namely the intervention group and the control group with equal number of subjects in each group. However, the intervention group had a distribution of subjects dominated by men (85%). Meanwhile, in the control group the proportions of both genders were the same. Statistical analysis showed that the gender characteristics of the two groups were significantly different, with a *P*-value of 0.020.

Based on age, these two groups had homogeneous characteristics where the mean age in the intervention group and the control group were 42 years and 43 years, respectively. Based on age groups of 18-45 years and 46-65 years, these two groups showed the same distribution, namely 11 subjects (55%) in the younger age group and 9 subjects (45 %) in the older age group. Statistical analysis showed that the age characteristics between the two groups were not statistically different (*P*= 1.000) and were homogeneous so that the sampling bias factor could be ignored.

Based on smoking status, there were more smokers in the intervention group than in the control group. Five of 13 people in the intervention group and 4 of 9 people in the control group had stopped smoking for more than 1 year. Approximately one third (35%) of the subjects in the intervention group and half (55%) of the subjects in the control group had never smoked at all or had smoked less than 100 cigarettes at the time of this sampling.

Table 1. Demographic Characteristics

Variable	Intervention n (%)	Control n (%)	*P*
Gender			*0.020*
Male	17 (85)	10 (50)	
Female	3 (15)	10 (50)	
Age (years old)			*1.000*
18-45	11 (55)	11 (55)	
46-65	9 (45)	9 (45)	
Mean	41±12.6	43±14.2	
Min	19	19	
Max	58	60	
Smoking Status			*0.631*
Former smoker	5 (25)	4 (20)	
Smoker	8 (40)	5 (25)	
Non-smoker	7 (35)	11 (55)	
Brinkman Index			*0.925*
Non-Smoker	7 (35)	11 (55)	
Mild	2 (10)	1 (5)	
Moderate	9 (45)	4 (20)	
Severe	2 (10)	4 (20)	
Mean	272	275	
Nutritional Status			*0.243*
Underweight	4 (20)	7 (35)	
Normal	14 (70)	11 (55)	
Overweight	2 (10)	2 (10)	
BMI (mean)	21.6	20.4	

Although there were more smokers in the intervention group than in the control group, the number of cigarettes smoked expressed as the Brinkman Index (BI) was higher in the control group, with a mean of 275. However, this difference was very small and not statistically significant (*P*= 0.925).

If further analysis was carried out where the magnitude of the BI was only assessed in the group that has smoked or in other words, the BI of those who have never smoked was excluded from the analysis, it was observed that the mean BI in the control group was much higher than the intervention group (580 vs 418). This might be related to the number of smokers with severe BI category, which was more common in the control group (44%), compared to the intervention group (15%). However, the increase in mean BI occurred evenly in all groups, and the statistical analysis did not indicate any significant differences (*P*= 0.210).

The nutritional status of the subjects in this study was generally good, with a mean BMI of 21.0. This value implied adequate or normal nutritional status. A similar picture was also seen in the intervention and control groups. The mean BMI in the intervention group was 21.6, while in the control group was 20.4, however, each was still within the normal range of BMI and adequate nutritional status. The intervention group had a mean BMI slightly higher than the control group. The control group had more study subjects with less nutritional status than the intervention group, namely 35% in the control group and 20% in the intervention group. On the other hand, these two groups had the same proportion of study subjects with excess nutritional status (10%). Despite the above conditions, statistical analysis indicated that the difference in nutritional status between the two groups was very small and not statistically significant (*P*= 0.243).

Table 2. The correlation between inspiratory muscle training using a respirometer and FEV_1

Group	FEV_1 *pre* (ml) (Mean±SD)	%Prediction (mean)	FEV_1 *post* (ml) (Mean±SD)	%Prediction (Mean)	Difference of FEV_1 *pre-post* (ml) (Mean±SD)	*P*
All (n= 40)	1615±553	59.6	1780±568	65.7	165±69	0.0001
Intervention (n=20)	1822±541	65.6	1996±554	71.9	175±80	0.0001
Control (n=20)	1409±496	54.1	1565±506	60.1	156±58	0.0001

Table 3. Correlation of inspiratory muscle exercise using a respirometer and FVC

Group	FVC *pre* (ml) (Mean±SD)	% Prediction (Mean)	FVC *post* (ml) (Mean±SD)	% Prediction (Mean)	Difference of FVC *pre-post* (ml) (Mean±SD)	*P*
All (n= 40)	1970±632	58.9	2210±676	66.1	240±102	0.0001
Intervention (n=20)	2170±631	63.6	2442±642	71.6	272±108	0.0001
Control (n=20)	1770±580	54.8	1979±643	61.3	209±87	0.0001

The pulmonary function tests among the subjects in this study showed a significant increase in FEV_1 and FVC after 6 days, both in the intervention group and control group.The FEV_1 value was appeared to increase in all subjects from 1615±553 ml (59,6% prediction) to 1780±568 ml (65,7% prediction) with *P*=0.0001, while the FVC value increased from 1970±632 ml (58.9% prediction) to 2210±676 ml (66.1% prediction) with *P*=0.0001.

Table 3 indicates that an increase in the FVC value occurred after 6 days in all study subjects (n=40) with a mean difference between pre-and post-evaluation FVC for 6 days of 240±102 ml (*P*= 0.0001). Table 2 and 3 shows the magnitude of the increase in FEV_1 and FVC values in the intervention and control groups after 6 days.

Although both groups represented an increase in FEV_1 and FVC values after 6 days of exercise/observation, the improvement in lung function in the intervention group was better than the control group. Table 4 exhibits that the increase in the FEV_1 value in the pre-and post-inspiratory muscle exercise of intervention group using a respirometer for 6 days was slightly higher than the control group with a mean difference of 19 ml where the difference in the mean FEV_1 value in the intervention group was 175±80 ml and the control group 156±58.

Nevertheless, this difference was not statistically significant (*P*=0.456). The increase in FVC value after 6 days of inspiratory muscle training using a respirometer in the intervention group was also greater than the control group with the difference in the intervention group of 272±108 ml and 209±87 ml in the control group. In contrast to the FEV_1 value, the difference in the FVC value in the intervention group compared to the control group showed a statistically significant difference (*P*=0.019).

Table 4. The correlation between inspiratory muscle training using a respirometer and lung function

Lung Function	Intervention	Control	*P*
FEV_1 (mean difference), ml	175±80	156±58	0.456
FVC (mean difference), ml	272±108	209±87	0.019

In the intervention group before the inspiratory muscle exercise, the majority of the subjects (60%) described the dyspnea severity as 'slightly short of breath' (Borg scale 0.5). Three subjects (15%) had a 'very mild shortness of breath' (Borg 1), and 1 subject (5%) had mild shortness of breath (Borg 2). Four subjects (20%) experienced 'no shortness of breath at all' (Borg scale 0). After inspiratory breathing muscle exercise using a respirometer for 6 days, there were improvements in the dyspnea severity. There were no subjects who were on the Borg 2 scale or Borg 1 scale. Most of the subjects (80%) felt 'no shortness of breath' (Borg scale 0), and only 4 subjects (20%) still felt 'slightly short of breath' (Borg scale 0.5). Statistical analysis indicated a significant improvement in the dyspnea severity after performing inspiratory muscle training using a respirometer for 6 days with *P*=0.0001.

Improvements in the dyspnea severity were also experienced by subjects in the control group who did not receive inspiratory muscle training using a respirometer. The majority of subjects (75%) in the control group at the beginning of the study felt 'slightly short of breath' (Borg scale 0.5). Two subjects (10%) complained of 'mild shortness of breath' (Borg 2), and 3 subjects (15%) experienced 'very mild' shortness of breath (Borg 1). None of the subjects experienced 'no shortness of breath at all' (Borg scale 0) at the beginning of the study.

After 6 days later, the dyspnea severity was re-assessed. Improvements were found as there were no more subjects in the Borg scale 1 and 2. In addition, the majority of the subjects (70%) already felt 'no shortness of breath at all' (Borg 0) and 6 subjects were still on Borg Scale 0.5 (slightly short of breath). The improvement in shortness of breath after 6 days of observation in the control group was also statistically significant (*P*=0.0001).

Table 5. The correlation between inspiratory muscle training using a respirometer and the dyspnea severity

Borg Scale	Intervention (n= 20)		Control (n= 20)		*P*
	Pre n (%)	*Post* n (%)	*Pre* n (%)	*Post* n (%)	
0	4 (20)	16 (80)	0 (0)	14 (70)	0.0001
0.5	12 (60)	4 (20)	15 (75)	6 (30)	
1	3 (15)	0 (0)	3 (15)	0 (0)	
2	1 (5)	0 (0)	2 (10)	0 (0)	

DISCUSSION

This study involved 40 study subjects who were homogeneously distributed in the intervention and control group. In other words, the two groups had similar demographic characteristics. This was expected to minimize sampling bias.

This study pointed out that TB pleurisy was more common in men than women. This was in line with previous studies, which explained that the prevalence of TB pleurisy was more common in men than women, with a ratio of 2:1. It could be associated with daily conditions where men were more exposed to TB risk factors such as smoking.[12]

The literatures stated that in countries with a high TB burden such as Indonesia, the incidence of pleural effusion complications in TB infection was more common at younger age with a mean age of 34 years, however, in developed countries, complications of pleural effusion in TB infection were more common at older ages.[13] In this study, the mean age of TB patients with pleural effusion was 42 years. This result was greater than the mean age of TB pleurisy in countries with a high TB burdenbut closer to the mean age of TB pleurisy in developed countries with low TB burdens of 49 years.[13]

The nutritional status of the study subjects was generally good, with a mean BMI of 21.0. Tuberculosis is often associated with malnutrition because of its effect on the immune system,[14] but the incidence of pleural effusion in TB is associated with better nutritional status. The previous study revealed that immune status affected the incidence of TB pleurisy. It was because the main mechanism of pleural effusion in TB patients was delayed hypersensitivity reactions. Therefore, immunocompromised individuals were less likely to develop TB pleurisy than immunocompetent individuals.[1]

Pleural effusion could cause shortness of breath, pleuritic chest pain, cough, and a feeling of pressure. This is directly related to the extent of the effusion which occurs. Shortness of breath with effusion is usually caused by hypoxemia resulting from intra-pulmonary shunting. The abnormality was not immediately corrected after thoracentesis.[5,15] It explained why the subjects in this study still experienced shortness of breath although the pleural fluid had been evacuated.

Pleural effusion could cause shortness of breath due to several factors such as impaired gas exchange, changes in respiratory mechanics such as decreased diaphragm, reduced efficiency of respiratory muscle function, and hemodynamic disturbances in massive pleural effusions. Thoracentesis can correct shortness of breath by restoring the abnormalities, but the actual mechanism is not fully understood.[16] The improvement in shortness of breath in this study could be caused by thoracentesis or inspiratory muscle training using a respirometer or a combination of both. To minimize the bias, dyspnea severity was measured after thoracentesis was completed.

Improvement of dyspnea progressed slowly post-thoracentesis in pleural effusion patients with a mechanism that is not fully understood. This improvement is characterized by improved lung function, increased work efficiency of the respiratory muscles, and particularly improvement in diaphragm function, which was previously depressed by the effusion fluid.[17] On the other hand, inspiratory muscle training using a respirometer could also improve the atelectasis in pleural effusions and help re-expanding the alveoli and air spaces that were previously closed.[9] These two factors influence the improvement of dyspnea previously felt by patients with pleural effusions. In addition, several other studies had also found that respirometers could improve lung function in patients with pleural effusion.[7]

There have been no studies assessing the dyspnea severity in pleural effusion patients using inspiratory muscle training, but there was a study which focused at how the use of respirometer could improve shortness of breath in COPD patients. The study assessed the dyspnea severity in COPD patients given respiratory muscle training with a portable device compared to those who received breathing exercise and incentive spirometry. Each

group performed exercises 2 times a day in 15 minutes daily for 5 days per week accumulated in 8 weeks. After 8 weeks, there were no significant difference between the improvement in dyspnea severity between the two groups, so it could be concluded that respiratory muscle training using a respirometer improved shortness of breath complaints as well as other respiratory muscle exercises in this case, namely the respiratory muscle training device.[18]

This study revealed that inspiratory muscle breathing exercises using a respirometer improved lung function by increasing the value of FEV_1 and FVC. In addition, the improvement in lung function in the intervention group was greater than in the control group, and this difference was also statistically significant.

A previous study that assessed lung function in pleural effusion patients who received respirometer exercise also found a similar finding. There was a significant increase in FEV_1 and FVC values after exercise using a respirometer compared to before exercise. In addition, Valenza, et al. showed that incentive spirometry and mobilization combined with chest drainage and medication in patients with pleural effusion led to better clinical improvement and shorter treatment periods. Statistical analysis comparing pre-and post-treatment spirometry parameters in patients receiving intervention pointed out significant changes in vital capacity, FEV_1, and forced expiratory flow values compared to the control group. The value of vital capacity increased from 73.1±12.6% to 72.13±13.7% (P< 0.001), while the FEV_1 value increased from 72.13±13.7% to 78.98±16.9% (P< 0.001). The value of forced expiratory currents also increased from 64.8±35.1% to 76.78±35.3%, although this last change was not statistically significant (P= 0.198). The duration of treatment was also shorter in the intervention group (26.7±8.8 days) compared to the control group (38.6±10.7 days) with P-value of 0.014.[7]

Respirometer is also able to improve lung function and to increase exercise capacity when combined with physical exercise. This was similar with the study conducted by Weiner, et al. that obtained a significant increase in lung function after 8 weeks of exercise in the intervention group, namely an increase in the FEV_1 value of 570 ml post lobectomy and 680 ml in post pneumonectomy cases compared to the previous predicted value.[11] Although this study was not impemented in cases of pleural effusion, it could more or less provide information about the role of respirometer in improving lung function.

Other literature stated that exercise using incentive spirometry or respirometer could be used to enable patients in breathing deeper and to increase respiratory capacity to restore collapsed alveoli and improve oxygenation. They observed that volume-oriented incentive spirometry resulted in a higher increase in lung volume than flow-oriented incentive spirometry, even though both resulted in the same lung and abdominal compartments displacement.[19] Incentive spirometry has been widely used for prevention and managing pulmonary complications following thoracic, cardiac, and abdominal surgery. However, a recent systematic review suggested that its benefits were controversial. They also mentioned that this was due to the poor quality of previous study methods.[20]

Another thing that could affect the assessment of the respirometer effectiveness was patient's adherence in using respirometer, both in terms of technique and frequency. For example, a study found the level of patient disobedience in using a respirometer reached 86.0%, with the excuse of forgeting (83.5%), not using it effectively (74.4%), and not performing the exercise with the instructed frequency (70.7%).[21] The success of exercise using a respirometer depends on the patient's adherence to the instructions. Unfortunately, one study obtained that poor adherence and suboptimal use could reduce the potential benefits of respirometers.[22] This study used persuasive and checklist methods to help improve patient compliance.

CONCLUSION

From the results of this study, there was a significant improvement in lung function and

shortness of breath after 6 days in all subjects, which was marked by an increase in the value of FEV_1 and FVC as well as the Borg scale either with or without inspiratory muscle training using respirometer. Although improvement in lung function was seen in both groups, the increase in FVC value after performing inspiratory muscle training using respirometer in the intervention group was greater. However, this exercise did not provide a significant increase in the FEV_1 value. Therefore, we conclude that inspiratory muscle exercise using respirometer improved lung function and could be considered as an additional therapy to assist lung expansion, particularly in patients with TB pleurisy.

REFERENCES

1. Jeon D. Tuberculous Pleurisy : An Update. Tuberc Respir Dis. 2014;3536:153–9.
2. Light RW. Update on tuberculous pleural effusion. Respirology. 2010;15(3):451–8.
3. Mitrouska I, Klimathianaki M, Mitrouska I, Klimathianaki M. Effects of pleural effusion on respiratory function. Can Respir J. 2004;11(7).
4. Krell W, Rodarte J. Effects of acute pleural effusion on respiratory system mechanics in dogs. J Appl Physiol. 1985;(59):1458–63.
5. Jardins T Des, Burton GG, Phelps TH. Clinical Manifestations and Assessment of Respiratory Disease. Seventh Ed. Elsevier; 2016.
6. Loscalzo J, Fauci AS, Kasper DL, Braunwald E, Hauser SL, Jameson JL, et al. Harrison's Pulmonary and Critical Care Medicine. McGraw Hill; 2010.
7. Valenza-Demet G, Valenza MC, Cabrera-Martos I, Torres-Sánchez I, Revelles-Moyano F. The effects of a physiotherapy programme on patients with a pleural effusion: A randomized controlled trial. Clin Rehabil. 2014;28(11):1087–95.
8. Ramírez-Sarmiento A, Orozco-Levi M, Güell R, Barreiro E, Hernandez N, Mota S, et al. Inspiratory muscle training in patients with chronic obstructive pulmonary disease: Structural adaptation and physiologic outcomes. Am J Respir Crit Care Med. 2002;166(11):1491–7.
9. Hiling L, Bakow E, Fink J, Kelly C, Sobush D, Southorn PA. Incentive Spirometry - AARC Clinical Practice Guideline. Respir Care J. 1991;36(12):1402–5.
10. Agarwal K, Solomen S. Comparative study between chest mobility exercises with incentive spirometry versus chest mobility exercises with stacked breathing on chest expansion in subjects with unilateral pleural effusion. Int J Dev Res. 2016;6(6):8034–8.
11. Weiner P, Man A, Weiner M, Rabner M, Waizman J, Magadle R, et al. The Effect of Incentive Spirometry and Inspiratory Muscle Training on Pulmonary Function After Lung Resection. J Thorac Cardiovasc Surg. 1997;113(3):552–7.
12. Yanti B, et al. Clinical and Demographic Characteristics Differences between M.tuberculosis and M.bovis Infection in Bronchiolveolar Lavage of Pulmonary Tuberculosis Patients. J Respirologi Indones. 2019;39(4):238–44.
13. Zhai K, Lu Y, Shi H. Tuberculous pleural effusion. J Thorac Dis. 2016;8(7):486–94.
14. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Vol. 2013, Pulmonary Medicine. Hindawi Publishing Corporation; 2013. p. 11.
15. Broaddus VC, Murray JF, Nadel JA, Mason RJ, Ernst JD, Lazarus SC, et al. Murray & Nadel's Textbook of Respiratory Medicine. 6th Editio. Broaddus C, editor. Elsevier; 2016.
16. Thomas R, Jenkins S, Eastwood PR. Physiology of breathlessness associated with pleural effusions. 2015;21(4):338–45.
17. Jindal S, Shankar P, Raoof S, Gupta D, Aggarwal AN, Agarwal R. Textbook of Pulmonary & Critical Care Medicine. First Edit. Jaypee Brothers Medical Publishers; 2011.
18. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier URS. Respiratory Muscle Endurance Training in Chronic Obstructive Pulmonary Disease Impact on Exercise

Capacity , Dyspnea , and Quality of Life. Am J Respir Crit Care Med. 2000;162:1709–14.

19. Paisani DDM, Lunardi AC, Cristine C, Marques B, Porras DC, Tanaka C, et al. Volume Rather Than Flow Incentive Spirometry Is Effective in Improving Chest Wall Expansion and Abdominal Displacement Using Optoelectronic Plethysmography. 2013;1360–6.
20. Carvalho C, Paisani D, Lunardi A. Incentive spirometry in major surgeries: a systematic review. NCBI. 2011;15(5):343–50.
21. Eltorai AEM, Baird GL, Eltorai AS, Pangborn J, Jr VA, Cullen HA, et al. Incentive Spirometry Adherence : A National Survey of Provider Perspectives. Respir Care. 2018;63(5).
22. Narayanan A, Hamid S, Supriyanto E. Evidence regarding patient adherence with incentive spirometry interventions after cardiac, thoracic and abdominal surgeries: A systematic review. Can Respir J. 2016;25(1):17–26.

Risk Factors of Prolonged QTc Interval in Patients with Drugs-Resistant Tuberculosis

Andika Pradana[1], Katharine[2], Parluhutan Siagian[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan

Abstract

Background*: Drug-Resistant Tuberculosis (DRTB) is still one of the biggest health problems worldwide. In 2016, WHO published new guidelines for DRTB management using 7 second-line drugs that only required 9-11 months of treatment with a higher success rate. Unfortunately, one of the side effects was the possibility of a prolonged QT-c interval on electrocardiography. However, to date there have been no known factors which increased the risk of QTc prolongation in DRTB patients.*

Methods: *This was a retrospective cohort study that analyzed the medical records of 50 DRTB patients who underwent treatment from August 2017 to August 2020 at the DRTB Clinic of Adam Malik Hospital Medan. Statistical analysis was performed using logistic regression to determine the factors which increased the risk of QTc prolongation in DRTB patients.*

Results: *Of the 50 study samples consisting of 40 MDR TB patients, 9 pre-XDR TB patients and 1 XDR TB patient, 14 (28%) subjects were found to have QTc prolongation. There were no correlation between the regimen type (*P *= 0.51), age (*P *= 0.40), sex (*P *= 0.74), nutritional status (*P *= 0.35) and comorbid diseases (*P *= 0.31) on the prolongation of QTc interval. Patients receiving clofazimine had a greater percentage (78.6% vs 21.4%) to experience prolonged QTc interval, although not statistically significant (*P *= 0.41).*

Conclusion: *Treatment regimen, age, sex, nutritional status and comorbid disease were not associated with prolonged QTc interval in DRTB.*
(J Respirol Indones 2022; 42(1): 52–7)

Keywords: *Regimen, prolonged-QTc, tuberculosis, resistant, electrocardiography*

Faktor Risiko Pemanjangan Interval QTc pada Pasien Tuberkulosis Resistan Obat

Abstrak

Latar Belakang: *Tuberkulosis Resisten Obat (TBRO) masih menjadi salah satu masalah kesehatan terbesar di dunia. Pada tahun 2016, WHO menerbitkan pedoman baru untuk manajemen TBRO menggunakan 7 obat lini kedua yang hanya membutuhkan 9-11 bulan pengobatan dengan tingkat keberhasilan yang lebih tinggi. Sayangnya, salah satu efek sampingnya adalah kemungkinan pemanjangan interval QT-c pada elektrokardiografi. Meski demikian, sampai saat ini belum ada faktor yang diketahui meningkatkan risiko pemanjangan QTc pada pasien TBRO.*

Metode: *Penelitian ini merupakan studi kohort retrospektif yang menganalisis rekam medis 50 pasien TBRO yang menjalani pengobatan sejak Agustus 2017 sampai Agustus 2020 di Klinik TBRO RS Adam Malik Medan. Analisis statistik dilakukan menggunakan regresi logistik untuk mengetahui faktor-faktor yang meningkatkan risiko pemanjangan interval QTc pada pasien TBRO.*

Hasil: *Dari 50 sampel penelitian yang terdiri dari 40 pasien TB MDR, 9 pasien TB pre-XDR dan 1 pasien TB XDR, terdapat 14 (28%) subjek yang mengalami pemanjangan interval QTc. Tidak ada hubungan antara jenis regimen (*P *= 0,51), usia (*P *= 0,40), jenis kelamin (*P *= 0,74), status gizi (*P *= 0,35) dan penyakit penyerta (*P *= 0,31) terhadap pemanjangan interval QTc. Pasien yang menerima clofazimin memiliki persentase yang lebih besar (78,6% vs 21,4%) untuk mengalami pemanjangan interval QTc, meskipun tidak bermakna secara statistik (*P *= 0,41).*

Kesimpulan: *Regimen pengobatan, umur, jenis kelamin, status gizi dan penyakit komorbid tidak berhubungan dengan pemanjangan interval QTc pada TBRO.* ***(J Respirol Indones 2022; 42(1): 52–7)***

Kata kunci*: regimen, interval QTc, tuberkulosis, resisten, elektrokardiografi*

Correspondence: Andika Pradana
Email: pradanaandika@gmail.com

INTRODUCTION

Tuberculosis (TB) is still one of the biggest health problems worldwide. Currently, the problem related to TB as a burden in the health sector is the high number of TB strains which are resistant to available TB drugs. Global TB Report 2020 by WHO stated that Indonesia had the second highest number of TB patients throughout the world.[1]

The success rate of TB treatment without complications in several country was actually quite good, reaching 86%. Unfortunately, this number has dropped dramatically in MDR TB cases as the success rate was only around 48%.[2] Moreover, in the case of XDR TB, the treatment success rate was very low, which was only 28%. Not to mention about the duration of treatment that reached 18–24 months, resulting in a greater number of failures and withdrawals.[3]

In 2016, WHO published new guideline for the management of drug resistant TB (DRTB). This guideline began to introduce a mixture of new treatments in the form of short-term regimen. This regimen used a combination of 7 second-line anti-tuberculosis drugs which only required 9–11 months of treatment with a higher treatment success rate than the previous conventional regimen.[4] Afterwards, in 2019, WHO introduced a fully oral regimen resulted in even better success rate.[5]

Unfortunately, one of the side effects that must be considered regarding the use of this regimen was the possibility of heart rhythm disturbances in the form of prolonged QTc interval (PQTcI) on electrocardiography. If it was not quickly identified, and thus not managed properly, this PQTcI would produce more serious adverse effects that might lead to death. The PQTcI reflects the delay in myocardial repolarization which is a predisposition of a rapid and chaotic heartbeat. This rapid heartbeat might trigger a sudden faint in patient. This polymorphic ventricular tachycardia is called torsades de pointes (TdP). Although usually self-limited, TdP may degenerate into ventricular fibrillation and cause syncope or even sudden death. In general, the QTc interval of more than 500ms is associated with an increased risk of fatal PQTcI.[6–10]

Several studies stated that PQTcI were reported to occur in 15–26% patients, but the exact number was still inconclusive.[10,11] More importantly, the data on the prevalence of PQTcI among DRTB patients in Indonesia was still not available. This study aimed to provide the number of DRTB patients who experienced PQTcI during treatment.

However, to date there have been no known factors that increase the risk of PQTcI in DRTB patients. Therefore, researchers were interested to identify factors that influenced the PQTcI in order to anticipate the possible side effects of heart rhythm disturbances.

METHODS

This was a retrospective cohort study that analyzed the medical records of 50 DRTB patients calculated by formula to estimate the proportion of population with specified relative precision. Study subjects were patients who underwent treatment from August 2017 to August 2020 at the DRTB Clinic RSUP H Adam Malik Medan. For this reason, a medical record review was carried out in order to follow the treatment course of DRTB patients from the beginning to the end of treatment with a focus on monitoring the QTc interval.

Electrocardiograph (ECG) was performed before treatment (baseline) and every month for the first 6 months of treatment. Assessment to determine the QTcI in this study was conducted in the fourth month. This was because data from previous studies stated that the highest incidence of prolonged QTc occurred in the first 4 months of treatment. Electrocardiograph interpretation was performed by certified cardiologist.

Ethical clearance was obtained from the Ethical Committee of Health Research Universitas Sumatera Utara. Statistical analysis was performed using logistic regression to determine the factors that might increase the risk of PQTcI in DRTB patients.

RESULTS

As many as fifty patients became the subjects of this study. Thirty-four patients (68%) were male. The majority of subjects were in the range of 30 to 59 years.

Table 1. Demographic characteristics of subjects

Characteristic		n	%
Sex	Male	34	68
	Female	16	32
Age	<30 years old	10	20
	30–59 years old	34	68
	≥60 years old	6	12
	Underweight	12	24
Nutritional status	Normoweight	36	72
	Overweight	2	4
Comorbid	Without comorbid	30	60
	DM	16	32
	HIV	4	8

This study was aim to determine factors that might induce PQTcI in DRTB patients. Therefore, all subjects underwent ECG examination every month. Assessment of the ECG results was performed by a certified cardiologist, in which QTc interval ≥500 ms was declared as prolonged. In this study, 14 subjects (28%) had PQTcI. The characteristics of subjects based on clinical appearance and ECG results can be seen in Table 2.

Table 2. Clinical characteristics of subjects

Characteristics		n	%
Prolonged QTcI	Yes	14	28
	No	36	72
Type of regimen	STR injection	19	38
	LTR oral	31	62
Diagnosis	MDR	40	80
	PreXDR	9	18
	XDR	1	2

STR Injection: Km – Mfx – Eto – Cfz – H(dt) – E – Z

LTR oral: Lfx – Bdq – Lzd – Cfz – Cs or Lfx – Bdq – Lzd – Cs – E

Km (Kanamycin), Mfx (Moxifloxacin), Eto (Etionamid), Cfz (Clofazimin), H(Isoniazid), E (etambutol), Z (Pirazinamid), Lfx (Levofloxacin), Bdq (Bedaquilin), Lzd (Linezolid), Cs (Cycloserine)

Statistical analysis was carried out to determine whether there was a correlation between clinical characteristics, treatment regimen and PQTcI, with the results as shown in Table 3.

Table 3 shows that there were no significant correlation between sex, age, nutritional status, and comorbidity to PQTcI in DRTB patients (P >0.05). There were also no association between the type of treatment regimen and PQTcI (P >0.05). However, it was obvious that of the 14 subjects experiencing PQTcI, 12 subjects received a regimen containing Clofazimine. Thus, the use of Clofazimine may increase the risk of PQTcI among DRTB patients.

Table 3 Factors associated with PQTcI

Characteristic		Prolonged		Normal		*P* value
		n	%	n	%	
Sex	Male	10	71.4	24	66.7	0.74
	Female	4	28.6	12	33.3	
Age	<30 years old	3	21.4	7	19.4	
	30–59 years old	8	57.1	26	72.2	0.407
	≥60 years old	3	21.4	3	8.3	
Nutritional status	Underweight	5	35.7	7	19.4	
	Normoweight	9	64.3	27	75.0	0.35
	Overweight	0	0.0	2	5.6	
Comorbid	Without comorbid	8	57.1	22	61.1	
	DM	6	42.9	10	27.8	0.31
	HIV	0	0.0	4	11.1	
Regimen	STR Injection	7	50.0	12	33.3	0.27
	LTR oral	7	50.0	24	66.7	
Mfx use	With Mfx	7	50.0	13	36.1	0.36
	Without Mfx	7	50.0	23	63.9	
Cfz use	With Cfz	12	85.7	25	69.4	0.23
	Without Cfz	2	14.3	11	30.5	
Bdq use	With Bdq	7	50.0	24	66.7	0.27
	Without Bdq	7	50.0	12	33.3	

DISCUSSION

Treatment regimens of DRTB continue to evolve over time. In 2016 WHO introduced a short-term regimen of 9–11 months with satisfying success rate.[4,12] Later in 2019, WHO introduced a full oral regimen which was declared to have a higher success rate.[5,13] Unfortunately, both the 2016 and the 2019 regimens contained a combination of several drugs that could cause PQTcI, including Bedaquiline, Delamanid, Clofazimine and Moxifloxacin.[6,7,14,15] In some cases, the PQTcI could be very severe and led to mortality.[9]

The QT interval is an ECG measure that represents the flow of ions through ventricular myocytes cell membrane mediated by specialized protein channels. When these channels do not work properly, they may disrupt normal heart rhythms and put patients at risk of life-threatening arrhythmias.[10,16]

This study aimed to identify factors associated with PQTcI in DRTB patients during treatment. Subjects of this study were grouped according to the type of treatment regimen they received. A total of 19 subjects received the WHO 2016 injectable short-term regimen/STR which consisted of Km - Mfx - Eto - Cfz - H (dt) - E – Z, meanwhile 31 subjects received the WHO 2019 full oral regimen, consisting of Lfx - Bdq - Lzd - Cs, with or without clofazimine (Cfz). Patients with QTc interval ≥500ms were declared to have a prolongation of QTc interval, both with and without clinical symptoms of cardiovascular disorders.[16]

Based on table 2, as many as 28% of subjects experienced PQTcI. In other words, nearly one-third of all DRTB patients experienced PQTcI during treatment. This finding was not much different from the previous studies which stated that the prevalence of PQTcI in DRTB patients ranged from 15–26%.[10,11]

Drug-associated QT prolongation is assumed to be caused by restraint of the rapid components and deferred rectifier potassium current. This restraint causes a prolongation of the length of the ventricular activity potential, leading to excessive sodium convergence or diminished potassium efflux. This induces a positive charge in the cell which can draw out the repolarization stage. This prolongation of the repolarization stage frequently causes a wavering of the layer expected known as ahead of schedule after depolarization. Repolarization stage stretching results in a drawn-out QT span on the ECG.[16,17]

Several studies have identified second-line antituberculosis drugs that could increase the risk of PQTcI. The drugs most reported to induce PQTcI were bedaquiline, delamanid, moxifloxacin or levofloxacin, and clofazimine.[10,16] Bedaquiline and delamanid produced metabolites M2 and DM6705 subsequently, causing QTc prolongation related to the inhibitory effect on the rapidly activating delayed rectifying potassium channels in myocardial tissue. The long terminal half-lives of M2 and DM6705 lead to a delayed effect of maximum QTc after 5–8 weeks of delamanid and 24 weeks of bedaquiline.[18] Moxifloxacin causes a slight prolongation of QTc by reversible and dose-dependent blockade of the rapidly activating delayed rectifying potassium channel. Moxifloxacin is more likely to cause prolonged QTc than the other fluoroquinolones. The risk of PQTcI with moxifloxacin is greater when electrolyte abnormalities occur. Clofazimine induces a PQTcI in a dose-dependent pattern.[19]

This study found that there were no significant difference in the incidence of PQTcI between subjects receiving bedaquilin, moxifloxacin or clofazimine regimens (P >0.05). However, of the 14 subjects receiving clofazimine, 12 (85.7%) subjects had PQTcI. This finding was much higher than that of bedaquiline and moxifloxacin where PQTcI was found in 50% of subjects. Thus, this study found that clofazimine was the DRTB drug most at risk for PQTcI. Another studies also stated that the use of DRTB drugs such as bedaquiline and moxifloxacin increased the risk of PQTcI when combined with clofazimine.[16]

However, there were some results that contradicted the findings of this study. Sanne, et al. stated that the incidence of PQTcI after clofazimine administration was fluctuating and influenced by

circadian rhythm, thus did not significantly cause PQTcI.[20] Another study stated that the effect of PQTcI due to clofazimine was related to the dose of the drug given, and it would return to normal after the drug was discontinued.[19]

This study found that there were no statistically significant correlation between sex (*P*=0.74), age (*P*=0.407), nutritional status (*P*=0.35) and comorbidities (*P*=0.31) with the incidence of PQTcI. Another study pointed out that patients aged >68 years and female sex could increase the risk of PQTcI which had the potential to cause Torsade de Pointes.[21]Further studies are needed to identify other factors associated with PQTcI such as electrolyte imbalance, dose of drug used and plasma drug concentration.

This study was funded by Universitas Sumatera Utara under the TALENTA Young Lecturer Research Scheme by 2020 Non-PNBP USU as stated in decree number 4142/UN5.1.R/PPM/2020 dated April 27, 2020.

CONCLUSION

The prolongation of QTc was found in 28% of DRTB patients. Drug-resistant TB patients who received a treatment regimen containing clofazimine were at greater risk of PQTcI although it was not statistically significant. There were no correlation between the treatment regimen, sex, age, nutritional status or comorbidities with PQTcI in DRTB patients. Regular monitoring of QTcI should be mandatory particularly in DRTB patients receiving regimens containing Clofazimine.

REFERENCES

1. World Health Organization. Global tuberculosis report 2020. World Health Organization. Geneva; 2020.
2. Kusmiati T, Mertaniasih NM, Eko Putranto JN, Suprapti B, Soedarsono, Luthfah N, et al. The role of C-Reactive protein as an inflammatory marker to predict prolonged QTc interval in rifampicin-resistant tuberculosis patients: A case-control study. Ann Med Surg. 2021 Oct;70:102899.
3. Lange C, Chesov D, Heyckendorf J, Leung CC, Udwadia Z, Dheda K. Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment. Respirology. 2018;23(7):656–73.
4. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017;49(3).
5. Jain NK. WHO consolidated guidelines on tuberculosis 2020 moving toward fully oral regimen: Should country act in hurry? Vol. 38, Lung India. Wolters Kluwer Medknow Publications; 2021. p. 303–6.
6. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: A systematic and critical analysis of the evidence. Eur Respir J. 2017;50(5):1701462.
7. Haverkamp W, Kruesmann F, Fritsch A, Veenhuyzen D van, Arvis P. Update on the Cardiac Safety of Moxifloxacin. Curr Drug Saf. 2012;7(2):149.
8. Guglielmetti L, Barkane L, Le Dû D, Marigot-Outtandy D, Robert J, Veziris N, et al. Safety and efficacy of exposure to bedaquiline-delamanid in multidrug-resistant tuberculosis: a case series from France and Latvia. Eur Respir J. 2018;51(3):1702550.
9. Trinkley KE, Lee Page R, Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: Essentials for clinicians. Curr Med Res Opin. 2013;29(12):1719–26.
10. Yoon H-Y, Jo K-W, Nam GB, Shim TS. Clinical significance of QT-prolonging drug use in patients with MDR-TB or NTM disease. Int J Tuberc Lung Dis. 2017;21(9):996–1001.
11. Asfaw MT, Holtzman DL, Kwan GF, Oyewusi LT, Mitnick CD, Seung KJ. Incidence of high grade qtcf prolongation and its management

among patients undergoing treatment for drug resistant tuberculosis (dr-tb): case series. African J Infect Dis. 2021;15(2):38–41.

12. Moodley R, Godec TR. Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials. Eur Respir Rev. 2016;25(139):29–35.
13. Pontali E, Raviglione MC, Migliori GB, Akkerman OW, Alffenaar JW, Blanc FX, et al. Regimens to treat multidrug-resistant tuberculosis: Past, present and future perspectives. Eur Respir Rev. 2019;28(152):190035.
14. Gupta R, Geiter LJ, Hafkin J, Wells CD. Delamanid and QT prolongation in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2015;19(10):1261–2.
15. Cohen K, Maartens G. A safety evaluation of bedaquiline for the treatment of multi-drug resistant tuberculosis. Expert Opin Drug Saf. 2019;18(10):875–82.
16. Harausz E, Cox H, Rich M, Mitnick CD, Zimetbaum P, Furin J. QTc prolongation and treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2015;19(4):385–91.
17. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89(11):1363–72.
18. Dooley KE, Rosenkranz SL, Conradie F, Moran L, Hafner R, von Groote-Bidlingmaier F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. Lancet Infect Dis. 2021;21(7):975–83.
19. Abdelwahab MT, Court R, Everitt D, Diacon AH, Dawson R, Svensson EM, et al. Effect of clofazimine concentration on qt prolongation in patients treated for tuberculosis. Antimicrob Agents Chemother. 2021;65(7):e0268720.
20. Zweijpfenning SMH, Van Groningen H, Van Ingen J, Magis-Escurra C, Boeree MJ, Wagner D, et al. Clofazimine does not lead to significant QT interval prolongation: A multicentre study. Eur Respir J. 2018;52(5):Clofazimine does not lead to significant QT interv.
21. Li M, Ramos LG. Drug-Induced QT Prolongation And Torsades de Pointes. Pharm Ther. 2017;42(7):473.

The Correlations Between Measurement of Lung Diffusing Capacity for Carbon Monoxide and the Severity Group of Asthma Patients in Persahabatan Hospital Jakarta

Bulkis Natsir, Faisal Yunus, Triya Damayanti

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

Abstract

Introduction: *Airway remodeling in asthma involving small airway can affect the alveoli and cause abnormalities in lung parenchyma. This study aimed to find lung parenchymal abnormalities in patients with asthma by examining diffusion capacity using the single breath DLCO method.*

Methods: *This was a cross-sectional study which divided asthma based on the degree of severity into two major groups, namely mild asthma (intermittent and mild persistent) and severe asthma (moderate and severe persistent). The number of each group was 31 subjects and 29 subjects, which were taken consecutively from stable asthma patients without comorbidities who were treated at Persahabatan Hospital during December 2015 - May 2016.*

Results: *The mean DLCO/prediction value in mild asthma group was 92.74±15.70% and while in the severe asthma group was 77.45±16.78%. Several spirometry values showed significant positive correlation with DLCO/prediction value, namely: FVC/prediction, FEV_1 /prediction and FEF25-75%/prediction with P<0.05. Correlation analysis showed FVC/prediction could dramatically affect the diffusion capacity of asthmatic patients. There was a significant correlation between lung function abnormalities (P=0,004) and the severity of asthma (P=0.000) with a corresponding decrease in DLCO/prediction (DLCO/prediction ≤75 %).*

Conclusion: *The severity of asthma had a correlation with the diffusion capacity of the lungs; the increasing severity led to a decrease in diffusion capacity of asthmatic patients. Decreased diffusion capacity showed that abnormalities in asthma occurred not only in the respiratory tract but also in the lung parenchyma.* ***(J Respirol Indones 2022; 42(1): 58-66)***

Keywords: *Asthma, lung diffusion, DLCO, airway remodeling*

Hubungan Pengukuran Kapasitas Difusi Paru Karbon Monoksida dengan Kelompok Keparahan Penderita Asma di RS Persahabatan Jakarta

Abstrak

Latar belakang: *Remodeling saluran napas pada asma yang melibatkan saluran napas kecil dapat mempengaruhi alveolus dan menyebabkan kelainan pada parenkim paru. Penelitian ini bertujuan mengetahui kelainan parenkim paru pada pasien asma melalui pemeriksaan kapasitas difusi menggunakan DLCO metode napas tunggal.*

Metode: *Penelitian ini merupakan uji potong lintang yang membagi asma berdasarkan derajat keparahannya menjadi dua kelompok besar, yaitu asma ringan (intermiten dan persisten ringan) dan asma berat (persisten sedang dan berat). Jumlah masing-masing kelompok adalah 31 subjek dan 29 subjek yang diambil secara berurutan dari pasien asma stabil tanpa penyakit penyerta yang berobat di RS Persahabatan selama bulan Desember 2015 - Mei 2016.*

Hasil: *Rerata nilai DLCO/prediksi pada kelompok asma ringan adalah 92,74±15,70% dan pada kelompok asma berat adalah 77,45±16,78%. Beberapa nilai spirometri menunjukkan korelasi positif yang bermakna dengan nilai DLCO/prediksi, yaitu: FVC/prediksi, FEV_1/prediksi dan FEF25-75%/prediksi dengan P<0,05. Analisis korelasi menunjukkan FVC/prediksi secara dramatis dapat mempengaruhi kapasitas difusi pasien asma. Terdapat hubungan bermakna antara kelainan fungsi paru (P=0,004) dengan beratnya asma (P=0,000) dengan penurunan DLCO/prediksi (DLCO/prediksi 75 %).*

Kesimpulan: *Derajat keparahan asma memiliki hubungan dengan kapasitas difusi paru; peningkatan keparahan menyebabkan penurunan kapasitas difusi pasien asma. Penurunan kapasitas difusi menunjukkan bahwa kelainan pada asma tidak hanya terjadi pada saluran pernapasan tetapi juga pada parenkim paru.* ***(J Respirol Indones 2022; 42(1): 58-66)***

Kata kunci: *Asma, difusi paru, DLCO, remodeling saluran napas*

Correspondence: Bulkis Natsir
Email: bulkis_natsir@gmail.com

INTRODUCTION

Asthma is characterized by increased airway reactivity. Patients with asthma have a recurrent or persistent airflow obstruction, either reversible or spontaneous.[1] However, the description of restriction can also be found in some patients. Decreased FVC due to air trapping results in pseudo-restriction on spirometry.[2] Several studies have also explored the possibility of impaired diffusion capacity in asthma by examining the carbon monoxide diffuse lung (DLCO).[3,4] Miller et al reported 32 (8%) patients of 413 patients with asthma experienced a restriction and impairment of DLCO, so it was concluded that restriction disorders could also occur in asthmatic patients.[2]

A study from Khan et al., observed a correlation between the length of asthma and decreased diffusion capacity.[5] Kharevich et al. also found a decrease in diffusion capacity in patients with severe asthma.[6] The theory of airway remodeling is considered to be responsible for persistent damage to the peripheral airways and plays ab indirect role in parenchymal damage in asthmatic patients.[7–9] This study attempted to identify the possible dysfunction of diffusion in asthmatic patients and the correlation to asthma severity.

METHODS

This was an analytic cross-sectional study conducted on asthmatic patients who were treated in Persahabatan Hospital from December 2015 to March 2016. The inclusion criteria were asthmatic patients based on medical records and willing to participate in the study. Exclusion criteria were pregnant women, patients with heart failure, patients with lung parenchymal damage (such as tuberculosis, bronchiectasis and interstitial lung diseases), deformities of the thoracic cavity and patients who refused to participate in the study.

Sampling was carried out by consecutive sampling on asthmatic patients in Persahabatan Hospital. Patient history was taken and physical examination was performed to determine whether the patients met the inclusion criteria. The patients were given information about the purpose of the study. If the patient was willing to participate in the study, the patients was asked to fill out a research consent letter.

Furthermore, the patients underwent spirometry and DLCO test. The latest chest X-ray was not required except for certain cases that obliged the latest radiographic confirmation based on the consideration of researchers. Adjustment of hemoglobin (Hb) for DLCO predictive values was not carried out so that the predictive value used the standard values according to the tools used. The data was then analyzed using the Statistical Package for Social Science (SPSS) 23.

RESULTS

The total subjects were 60 people, divided into two groups based on the severity of asthma, namely 31 subjects of mild asthma and 29 subjects of severe asthma.

Table 1. Characteristics of subjects

Variable	Asthma Group			
	Mild		Severe	
	n	%	n	%
Gender				
Male	3	9.7	6	20.7
Female	28	90.3	23	79.3
BMI				
Underweight	0	0	0	0
Normal	12	38.7	12	41.4
Overweight	3	9.7	7	24.1
Obese class I	10	32.1	9	31
Obese class II	6	19.4	1	3.4
Exacerbation history				
Yes	10	32.3	17	58.6
No	21	67.7	12	41.4
Degree of asthma control				
Uncontrolled	7	22.6	15	51.7
Partially controlled	13	41.9	14	48.3
Completely controlled	11	35.5	0	0
Duration of asthma				
<30 years	26	83.9	10	34.5
≥30 years	5	16.1	19	65.5
Steroid history				
Yes	22	71	29	100
No	9	29	0	0
Smoking habits				
Yes	1	3.2	1	3.4
No	30	96.8	28	96.6
Asthma control test				
1–20	10	32.3	15	51.7
21–24	10	32.3	14	48.3
25	11	35.5	0	0
Spirometry				
Normal	13	41.9	0	0
Obstruction	15	48.4	14	48.3
Restriction	3	9.7	0	0
Mixed	0	0	15	51.7

The mild asthma group consisted of intermittent asthma and mild persistent asthma, while the severe asthma group consisted of moderate and severe persistent asthma. In two groups, most of the subjects were female: 28 subjects (90.3%) in mild asthma group and 23 subjects (79.3%) in severe asthma group. The details can be seen in Table 1.

Table 2. The mean value of age, spirometry and DLCO test

Variable	Mild-Moderate Asthma	Severe Asthma
	Mean (SD)	Mean (SD)
Age (years)	39.58 (13.89)	49.00 (13.93)
FVC (milliliter)	2518 (692.15)	1892 (592.66)
FVC (%)	97.51 (15.01)	77.45 (16.78)
FEV_1 (milliliter)	1980.00 (644.03)	1142 (360.06)
FEV_1 (%)	90.12 (15.67)	56.82 (14.35)
FEV_1/FVC	77.26 (8.50)	60.58 (7.98)
$FEF_{25–75}$ (liter/second)	1.72 (0.57)	0.64 (0.32)
$FEF_{25–75}$ (%)	58.41 (14.82)	24.31 (9.20)
PEF (liter/second)	5.36 (1.38)	3.39 (1.24)
DLCO (ml/minute/mmHg)	21.92 (4.81)	17.85 (4.28)
DLCO (%)	92.74 (15.70)	78.41 (14.21)
AV (liter)	3.82 (0.72)	3.35 (1.02)
AV (%)	89.61 (13.73)	80.38 (15.79)
KCO (ml/minute/mmHg/L)	5.78 (0.92)	5.40 (0.81)
KCO (%)	104.90 (16.61)	99.27 (16.25)
KPT (liter)	4.02 (0.76)	3.50 (1.02)
KPT (%)	89.64 (13.45)	81.13 (15.11)

Note: Data presented as mean; FEV_1=forced expiratory volume in one second; %pred=%predicted; FVC=forced vital capacity; FEF=forced expiratory flow 25–75 second; PEF=peak expiratory flow; DLCO=diffuse lung carbon monoxide; AV=alveolar volume; KCO=carbon monoxide diffusion constant; TLC=total lung capacity.

The mean FVC/prediction in mild asthma group was 97.51±15.01%, indicating a normal value (FVC/prediction >80%) while in the severe asthma group it was lower (77.45±16.78%). The mean FEV_1/prediction in mild asthma group also showed a normal value of 90.12±15.67% and it was decreased in the severe asthma group with 56.82±14.35%.

The mean FEV_1/FVC showed normal value (FEV_1/FVC >75%) in mild asthma group of 77.26±8.50%. In the severe asthma group, the mean FEV_1/FVC indicated a description of obstruction with 60.58±7.98%. Diffusion capacity described by DLCO/prediction showed a normal value in mild asthma group of 97.24±15.70% and slightly lower in the severe asthma group of 78.41±14.21%.

Table 3. The correlation of subject characteristics with DLCO

Variable	DLCO/prediction		*P*
	Mean (%)	SD	
Gender			
Male	78.22	18.42	0.136
Female	87.16	16.00	
BMI			
Underweight	0	0	
Normal	80.54	15.11	
Overweight	85.00	18.09	0.051
Obese class I	87.42	17.86	
Obese class II	85.72	8.00	
Exacerbation history			
Yes	87.61	16.93	0.359
No	83.62	16.08	
Degree of asthma control			
Well controlled	94.63	14.99	
Partly controlled	83.70	16.75	0.147
Uncontrolled	84.00	16.25	
Duration of asthma			
<30 years	88.25	18.71	0.165
≥30 years	82.16	12.05	
Steroid history			
Yes	85.22	17.06	0.507
No	89.22	13.45	
Smoking habits			
Yes	82.00	4.24	0.743
No	85.95	16.79	
Asthma control test			
1–20	84.85	15.53	
21–24	82.59	17.59	0.131
25	94.64	14.99	

Several variables had a close significance with *P*<0.05 compared to other factors namely BMI (*P*=0.051), gender (*P*=0.136), the degree of asthma control (*P*=0.147) and ACT (*P*=0.131).

Table 4. The correlation between age and spirometry with DLCO/prediction

Variable	R	*P*
Ages	-0.055	0.678
FVC/prediction	0.505	0.0001
FEV_1/prediction	0.409	0.001
FEV_1/FVC	0.207	0.113
$FEF_{25–75}$/prediction	0.279	0.031

Based on the mean analysis, we found no significant correlation between age (*P*=0.678), FEV_1/FVC (*P*=0.113) and DLCO/prediction value. On the other hand, FVC/prediction, FEV_1/prediction and FEF25–75%/prediction showed significant positive correlation.

Table 5. The correlation between lung function with decreased diffusion capacity

Spirometry	DLCO value/prediction		Total	*P*
	Normal (>75%)	Decreased (≤75%)		
Normal	12 (20%)	1 (1.7%)	13	0.001
Obstruction	23 (38.3%)	6 (10%)	29	
Restriction	3 (5%)	0 (0%)	3	
Mixed	5 (8.3%)	10 (16.7%)	15	
Total	43 (71.7%)	17 (28.3%)	60	

Lung function becomes one of the basis for determining the severity of asthma. We observed43 subjects (71.7%) with normal diffusion capacity and the remaining 17 subjects (28.3%) with decreased diffusion capacity in our study. We obtained a significant correlation between lung function and decreased diffusion capacity.

On the association between asthma severity and a decline in DLCO/prediction, we found that the mild asthma group had 28 subjects (93.3%) with normal diffusion capacity and 2 subjects (6.7%) with decreased diffusion capacity, while severe asthma group had each 15 subjects (50%) with normal and reduced diffusion capacity.

The results of this study indicated that there was a significant relationship between the severity of asthma and decrease in DLCO/prediction with *P*=0,0001.

Table 6. Correlation between severity of asthma and decline of DLCO/prediction

Asthma Group	DLCO value/prediction		Total	*P*
	Normal (>75%)	Decreased (≤75%)		
Mild-moderate asthma	29 (96.7%)	2 (3.3%)	31	0.0001
Severe asthma	14 (46.7%)	15 (53.3%)	29	

DISCUSSION

This study aimed to determine the factors that influenced the diffusion capacity in asthma through DLCO test. We found that gender had no significant correlation with *P*=0.136. This could be due to the small number of male subjects in both groups of asthma, namely 3 subjects (9.7 %) in the mild asthma group and 6 subjects (20.7%) in the severe asthma group. Neder et al. stated similar result with no significant correlation between the genders, although the mean DLCO was higher in men than women.[4] Marco et al concluded that the high incidence of asthma in women might be caused by hormonal changes during pubertal phase.[10] Other studies mentioned that pregnancy, use of oral contraceptives and hormonal therapy have shown that hormonal factors played a role in the severity of exacerbations and asthma.[11–13]

Body mass index also had no significant correlation with the value of DLCO/prediction (*P*=0.051) in asthmatic patients, although more than half of the subjects with normal body weight were exceeded. This may be due to the absence of evenly distributed number of subjects between each BMI category. Neder et al. pointed out that weight gain was positively associated with DLCO value but could not be a predictor that individually affected DLCO when added with age and height.[4]

Khan et al. conducted a study on subjects who had been diagnosed with asthma for 30 years and found that 89% of the subjects were obese.[5] Obese subjects with asthma had a large frequency in many studies with risk of developing asthma increasing by 50%.[14–16] Obesity in asthma lowers the response to asthma medications including corticosteroids. Other mechanisms related to the effects of obesity on the mechanical motion of the chest wall and the airway, noneosinofilic airway inflammation, extrapulmonary inflammation involving systemic components and adipose tissues of asthmatic patients.[17]

Past exacerbation history, degree of asthma control and ACT also had no significant correlation with the diffusion capacity. These three variables are able to give a description of how severe the asthma of the patient is. Intermittent asthma and mild persistent asthma may reflect normal lung function beyond an asthma attack, in contrast to severe persistent asthma. However, inhomogeneous severity of asthma might play a role in the results of the analysis of these three variables.

More than half of the patients had used inhaled corticosteroids (ICS) as a controller, especially in the severe asthma group, but we obtained mean FEV_1/prediction of 56.82±14.35%, mean FEV_1/FVC of 60.58±7.98% and decreased diffusing capacity in 15 subjects. This indicated a

persistent decline in lung function despite the ICS use. Khan et al. observed similar results and suggested that airway remodeling persisted despite taking steroids as a controller.[5] Nevertheless, this study did not find a statistically significant correlation between the ICS use and DLCO/prediction value. It could be due to the absence of data regarding the duration of steroids use and the steroids doses, as well as the inhomogeneity of asthma severity in the subjects.

This study obtained a mean value of DLCO/prediction in subjects who had been diagnosed with asthma less than 30 years of 88.25% and a slight decrease in subjects diagnosed with asthma over 30 years of 82.16%. Both still had a normal mean DLCO/prediction, in line with the results of this study which stated that there were no significant correlation between the length of time diagnosed with asthma and the DLCO/prediction value (*P*=0.165). The inhomogeneous severity of asthma might possibly be the cause of these results. A person may have long been diagnosed as having intermittent or mild persistent asthma in good control, so that they do not have irreversible pulmonary function abnormalities. Khan et al. examined asthmatic patients who had been diagnosed with asthma for more than 30 years and found only 6% of subjects with increased diffusion capacity, 57% with decreased diffusion capacity and the rest were within normal limits, however, they did not look for the correlation between duration of asthma and DLCO/prediction value.[5]

Smoking had no significant correlation with the value of DLCO/prediction (*P*=0.743). This could be due to our study only earned1 subject (3.3%) of mild asthma group and 1 subject (3.3%) of severe asthma group who had a history of smoking with mild Brinkman index. Longitudinal studies regarding reduction in diffusion capacity have failed to show a significant correlation between the DLCO test result with smoking status, but indicates that active smokers have a low value of DLCO/prediction.[18,19] Matheson et al. also found similar results that only the still smokers were linked to reduced diffusion capacity with or without resistance in the airways.[20] Smoke inhalation in animals and humans showed an increment in pulmonary artery pressure and it was considered as a result of pulmonary capillary vasoconstriction due to nicotine, thus contributing to the decline in pulmonary diffusion capacity.[21–23] Diffusion capacity alteration due to changes of membrane diffusion or blood volume in the capillaries and a variety of conditions will reduce the surface area of membrane diffusion, such as alveolar structural damage that occurs in emphysema.[24]

This study showed that there was a significant correlation between some spirometry values and lung diffusion capacity while Collard et al. obtained a dissimilar result.[25] The FVC/prediction value had a significant positive relationship with the value of DLCO/prediction (*P*=0.0001), although predictions had a weak strength (r<0.5). The mean FVC/prediction especially in the severe asthma group of this study described restriction in patients with asthma. Description of restriction also reported by Colp et al. which was seen as a reversible closure of the airway.[24] Miller et al. found one third of study subjects (33 of 100 subjects) had restrictions with a decrease in diffusion capacity but without clinical symptoms and radiographic evidence of disease or vascular/interstitial disease. Miller et al. also emphasized that obesity might be one of the factors which influenced restrictions in asthma.[2] Most study had a high prevalence of obesity in asthma.

In the severe asthma group impairment in FEV_1/prediction was observed with 56.82±14.35% and resulted in positive correlation that was weak but significant with value of DLCO/prediction. The more severe obstruction will further lower diffusion capacity. It was slightly different from the FEV_1/FVC value which showed a positive but not significant correlation (*P*=0.09) with the value of DLCO/prediction. Khan et al found no significant correlation between worsening or increasing FEV_1 with DLCO/predictionvalue.[5] This was caused by FEV_1 abnormalities which were more representative for the impairment in the large airways (conduction zone) than small airways such as the respiratory

bronchioles which was part of the respiratory zone of the lung.

The value of FEF25-75%/prediction also indicated a significant positive correlation with the value of DLCO/prediction (*P*=0.026). Kenneth et al. conducted study in asthmatic patients and found irreversible decline in FEF25-75%/prediction, which was a marker of small airway damage.[26] Sobonya et al. analyzed lung tissue biopsy specimens from six non-smoking severe asthma patients with a history of allergic asthma and who died not of status asthmaticus. They found that two of these patients had small airways inflammation and fibrosis in the trachea wall.[27]

This study achieved a significant correlation between lung function abnormalities and decreased diffusion capacity (*P*=0.001). Decreased diffusion capacity was found in 17 subjects (28.3%) with a description of normal lung function in 1 subject (1.7%), obstruction in 6 subjects (10%) and the remaining 10 subjects (16.7%) had mixed abnormal lung function (obstruction and restriction). Restriction abnormalities in asthma according to Keddissi et al. were caused by rapidly reversible airway closure resulting in air trapping and low FVC.[28]

Miller et al proved that there was restriction in 33% of subjects (33 of 100) with asthma accompanied by decreased diffusion capacity without evidence of pulmonary vascular and tissue abnormalities.[2] The more severe decline in lung function got along with a decrease in DLCO. Khan et al. obtained a reduction in diffusion capacity in 37 of 65 subjects (57%) weight loss occurred in 6 subjects but did not find an association between FEV1 with DLCO values.[5] Kharevich et al. concluded from their study on the diffusion capacity in asthma that persistent airflow limitation, air trapping and decreased diffusion capacity could occur in patients with severe asthma. This might be due to airway remodeling and structural changes in the lung parenchyma, thickening of the diffusion membrane and diminution of outer lung surface.[6]

This study found that two of 31 subjects (3.3%) in the mild asthma group experienced a decline in DLCO/prediction, whereas in the severe asthma group the decline was observed in 15 of 29 subjects (53,3%). The data showed that two subjects had decreased diffusion capacity in the mild asthma group, namely mild persistent asthma. One subject had obesity and mild restriction while the other subject had normal BMI and mild obstruction. The main limitation of this study was that the researchers did not perform further evaluation with chest X-ray or CT scan which could help finding the cause of decreased diffusion capacity in mild asthma group.

This study obtained a significant positive correlation between asthma severity and decreased diffusion capacity. The more severe the asthma severity, the more likely it was to experience DLCO/prediction impairment with a *P*-value of 0.000 (*P* <0.5). This result was in contrast to the study from Ohman et al. who pointed out normal or increased diffusion capacity in asthmatic patients.[29] They believed that the escalation in diffusion capacity was not caused by an elevation in pulmonary capillary flow (Vc). The increased diffusion capacity in asthma might be due to an increment in surface area and a decline in the thickness of pulmonary alveolar-capillary membrane due to hyperinflation, but this was not the only reason. The limitation of study from Ohman et al. was the number of subjects that was less than 10 stable asthmatic patients and there were no information regarding the severity of asthma in the subject which might explain the absence of impairment in diffusion capacity.[29]

Kharevich et al. who divided the study subjects into mild and severe asthma groups based on WHO criteria for severe asthma also gained impaired diffusion capacity in severe asthma group with *P*=0.008. They then concluded that there have been structural changes in airway remodeling and lung parenchyma in patients with severe asthma.[6] Similar to Miller et al., 8% of the subjects who reported asthma of varying severity and duration of diagnosed asthma had lower DLCO/prediction values even after removing all confounding factors.[2] This was on the contrary to Girodet et al. who

investigated the basement membrane remodeling of the respiratory tract in mild asthma patients and found an increase in the number of mitochondria even in patients with mild asthma. In some patients, elevated mitochondrial biogenesis is the key to augmented cell proliferation and basement membrane remodeling.[30]

Various studies of asthma in recent years have uncovered that the inflammatory process extends from the large airways to the peripheral airways and lung parenchyma. These studies indicated that severe inflammation and structural changes also occur in the small airways and lung parenchyma.[31–33] This was observed from specimens of asthmatic patients taken through resection of lung tissue, lung autopsy specimens and transbronchial biopsies.[34–36] Peripheral airways including lung tissue were recognized as the dominant areas of airway obstruction in asthmatic patients.[37–39]

Wagner et al. stated that mild asthmatic patients with normal spirometry had an approximately sevenfold increase in peripheral airway resistance compared with controls and this was associated with the response to methacholine.[40] Carrol et al. investigated the distribution of inflammatory cells along the bronchial tree in both fatal and non-fatal asthma cases.[41] They noticed a uniform increment in eosinophils in the large and small airways among mild and severe asthma compared with controls. Comparison of large and small airways exhibited an escalation in the number of eosinophils in airway diameter of less than 2 mm which proved that the inflammatory process also occured in small airways.

CONCLUSION

In summary, this study identified that there was a significant correlation between severity of asthma and decreased diffusion capacity of asthmatic patients. However, this study needs to do further research with a larger number of samples and representing each degree of asthma in the same amount. Diffusion capacity examination should be done regularly, especially in patients with severe asthma.

REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2014. *Glob Initiat Asthma*. 2014:2-80.
2. Miller A, Palecki A. Restrictive impairment in patients with asthma. *Respir Med*. 2007;101(2):272-276.
3. Mishima M. Physiological differences and similarities in asthma and COPD--based on respiratory function testing. *Allergol Int*. 2009;58(3):333-340.
4. Neder JA, Andreoni S, Castelo-Filho A, Nery LE. Reference values for lung function tests. I. Static volumes. *Brazilian J Med Biol Res*. 1999;32(6):703-717.
5. Khan Z, Miller A, Bachan M, et al. Clinical status and pulmonary function in patients with long standing (more than 30 years) asthma. *Int J Med Med Sci*. 2012;4(9):200-203.
6. Kharevich O, Lapteva I, Lapteva E, Tomashevsky A, Koroleva E. Air-trapping and decreased diffusion capacity in patients with severe asthma. *Eur Respir J*. 2012;40(Suppl 56):P505.
7. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol*. 2008;8(3):183-192.
8. Yamauchi K, Inoue H. Airway remodeling in asthma and irreversible airflow limitation - ECM deposition in airway and possible therapy for remodeling. *Allergol Int*. 2007;56(4):321-329.
9. Postma DS, Timens W. Remodeling in asthma and chronic obstructive pulmonary disease. In: *Proceedings of the American Thoracic Society*. Vol 3. ; 2006:434-439.
10. de Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med*. 2000;162(1):68-74.

11. Alberts WM. “Circa Menstrual” Rhythmicity and Asthma. *Chest*. 1997;111(4):840-842.
12. Gibbs CJ, Coutts II, Lock R, Finnegan OC, White RJ. Premenstrual exacerbation of asthma. *Thorax*. 1984;39(11):833-836.
13. Beynon HL, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. *Lancet (London, England)*. 1988;2(8607):370-372.
14. Gwynn RC. Risk factors for asthma in US adults: results from the 2000 Behavioral Risk Factor Surveillance System. *J Asthma*. 2004;41(1):91-98.
15. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007;175(7):661-666.
16. Beckett WS, Jacobs DRJ, Yu X, Iribarren C, Williams OD. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med*. 2001;164(11):2045-2050.
17. Gibson PG. Obesity and asthma. *Ann Am Thorac Soc*. 2013;10(SUPPL):138-142.
18. Neas LM, Schwartz J. The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. *Am J Respir Crit Care Med*. 1996;153(2):656-664.
19. Sansores RH, Pare P, Abboud RT. Effect of smoking cessation on pulmonary carbon monoxide diffusing capacity and capillary blood volume. *Am Rev Respir Dis*. 1992;146(4):959-964.
20. Matheson MC, Raven J, Johns DP, Abramson MJ, Walters EH. Associations between reduced diffusing capacity and airflow obstruction in community-based subjects. *Respir Med*. 2007;101(8):1730-1737.
21. Knudson RJ, Kaltenborn WT, Burrows B. The effects of cigarette smoking and smoking cessation on the carbon monoxide diffusing capacity of the lung in asymptomatic subjects. *Am Rev Respir Dis*. 1989;140(3):645-651.
22. Van Ganse WF, Ferris BGJ, Cotes JE. Cigarette smoking and pulmonary diffusing capacity. (Transfer factor). *Am Rev Respir Dis*. 1972;105(1):30-41.
23. Mohammed NH. Lung Diffusing Capacity for Carbon Monoxide (DLco-SB): the Influence of Cigarette Smoking. *Iraqi Postgrad Med J*. 2010;9(3):328-334.
24. Colp C, Williams MHJ. Total occlusion of airways producing a restrictive pattern of ventilatory impairment. *Am Rev Respir Dis*. 1973;108(1):118-122.
25. Collard P, Njinou B, Nejadnik B, Keyeux A, Frans A. Single breath diffusing capacity for carbon monoxide in stable asthma. *Chest*. 1994;105(5):1426-1429.
26. Backman KS, Greenberger PA, Patterson R. Airways Obstruction in Patients With Long-term Asthma Consistent With Irreversible Asthma’. *Chest*. 1997;112(5):1234-1240.
27. Sobonya RE. Quantitative structural alterations in long-standing allergic asthma. *Am Rev Respir Dis*. 1984;130(2):289-292.
28. Keddissi JI, Elya MK, Farooq SU, et al. Bronchial Responsiveness in Patients with Restrictive Spirometry. Bouros D, ed. *Biomed Res Int*. 2013;2013:498205.
29. Ohman JL, Schmidt-Nowara W, Lawrence M, Kazemi H, Lowell FC. The Diffusing Capacity in Asthma. *Am Rev Respir Dis*. 1973;107(6):932-939.
30. Girodet P-O, Allard B, Thumerel M, et al. Bronchial Smooth Muscle Remodeling in Nonsevere Asthma. *Am J Respir Crit Care Med*. 2016;193(6):627-633.
31. Tulic MK, Christodoulopoulos P, Hamid Q. Small airway inflammation in asthma. *Respir Res*. 2001;2(6):333-339.
32. Faul JL, Tormey VJ, Leonard C, et al. Lung immunopathology in cases of sudden asthma death. *Eur Respir J*. 1997;10(2):301-307.
33. Synek M, Anto JM, Beasley R, et al. Immunopathology of fatal soybean dust-induced asthma. *Eur Respir J*. 1996;9(1):54-57.
34. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med*.

1996;154(5):1505-1510.

35. Hamid Q, Song Y, Kotsimbos TC, et al. Inflammation of small airways in asthma. *J Allergy Clin Immunol*. 1997;100(1):44-51.
36. Minshall EM, Hodd JC, Hamid QA. Cytokine mRNA expression in asthma is not restricted to the large airways. *J Allergy Clin Immunol*. 1998;101(3):386-390.
37. Taha RA, Minshall EM, Miotto D, et al. Eotaxin and monocyte chemotactic protein-4 mRNA expression in small airways of asthmatic and nonasthmatic individuals. *J Allergy Clin Immunol*. 1999;103(3):476-483.
38. Christodoulopoulos P, Leung DYM, Elliott MW, et al. Increased number of glucocorticoid receptor-β–expressing cells in the airways in fatal asthma. *J Allergy Clin Immunol*. 2000;106(3):479-484.
39. Ingram RHJ. Physiological assessment of inflammation in the peripheral lung of asthmatic patients. *Lung*. 1990;168(5):237-247.
40. Wagner EM, Bleecker ER, Permutt S, Liu MC. Direct assessment of small airways reactivity in human subjects. *Am J Respir Crit Care Med*. 1998;157(2):447-452.
41. Carroll N, Carello S, Cooke C, James A. Airway structure and inflammatory cells in fatal attacks of asthma. *Eur Respir J*. 1996;9(4):709-715.

Safety of Favipiravir for Treatment of COVID-19: Latest Systematic Review

Rizki Oktarini[1], Anna Rozaliyani[2], Ratika Rahmasari[1], Muhammad Alkaff[3], Rani Sauriasari[1]

[1]Faculty of Pharmacy, Universitas Indonesia, Depok
[2]Parasitology Department, Faculty of Medicine, Universitas Indonesia, Depok
[3]Department of Internal Medicine, Persahabatan Central General Hospital, Jakarta

Abstract

***Background**: Adverse event studies of favipiravir used to treat COVID-19 have been ongoing since it was established as a treatment option. A better understanding of the side effects of favipiravir from recent studies is important for developing and assessing the introduction of effective treatments for COVID-19.*
***Method:** The author conducted a systematic review based on research studies and case reports on favipiravir monotherapy in COVID-19. Access to the included studies is via PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv.*
***Results:** Twelve studies consisting of eight research studies and four case reports were reviewed. The most common side effects were diarrhea, elevated liver enzyme levels, and hyperuricemia. None of which were significantly different from the comparison. Currently, various adverse event was reported in case reports such as drug fever, acute generalized exanthematous pustulosis (AGEP), and transient increase in viral load. The side effects mostly will recover after the treatment is discontinued.*
Conclusion:** The use of favipiravir to treat COVID-19 causes dose-related side effects such as diarrhea, changes in liver enzymes, and increased uric acid. Nothing is important when compared to other antiviral drugs. To improve the efficacy and safety of COVID-19 therapy, it is important to prepare an incidence report of antiviral adverse events in special populations such as children, pregnant women, and organ dysfunction. **(J Respirol Indones 2022; 42(1): 67-75)
***Keyword**: Favipiravir, SARS-Cov-2, COVID-19, adverse event, side effects.*

Keamanan Favipiravir untuk Terapi COVID-19: Tinjauan Sistematis Terbaru

Abstrak

***Latar belakang**: Pemahaman yang lebih baik tentang efek samping antivirus favipiravir dari penelitian saat ini penting untuk mengembangkan dan menilai pengenalan pengobatan yang efektif untuk COVID-19.*
***Metode:** Penulis melakukan tinjauan sistematis terhadap uji klinis dan laporan kasus monoterapi favipiravir dalam pengobatan COVID-19. Akses ke studi yang disertakan adalah melalui PubMed, SCOPUS, Science Direct, SpringerLink, dan MedRxiv.*
***Hasil:** Dua belas studi, terdiri dari delapan studi efikasi dan empat laporan kasus, memenuhi kriteria penulis. Efek samping yang paling umum adalah diare, peningkatan kadar enzim hati, dan hiperurisemia. Tidak terdapat perbedaan yang signifikan dari perbandingan. Saat ini, berbagai efek samping dilaporkan dalam laporan kasus seperti demam obat, pustulosis eksantematosa umum akut (AGEP), serta peningkatan viral load sementara. Efek samping sebagian besar akan pulih setelah pengobatan dihentikan.*
Kesimpulan:** Penggunaan favipiravir untuk mengobati COVID 19 memiliki efek samping seperti diare, perubahan enzim di siang hari, dan peningkatan asam urat yang reversibel. Efek samping yang terjadi juga kurang penting dibandingkan obat antivirus lainnya. Membuat laporan tentang terjadinya efek samping antivirus pada populasi khusus seperti anak-anak, wanita hamil, dan disfungsi organ penting untuk meningkatkan terapi COVID-19 yang efektif dan aman. **(J Respirol Indones 2022; 42(1): 67-75)
***Kata kunci:** Favipiravir, SARS-Cov-2, COVID-19, adverse event, side effects.*

Corresponding author: Rani Sauriasari
Email: rani@farmasi.ui.ac.id

INTRODUCTION

SARS-coronavirus-2 (SARS-CoV-2) emerged in Hubei, China in past due 2019 as a reason of acute respiration misery syndrome and respiration contamination which could cause death (COVID-19).[1,2] Older age, male sex, smoking, and the presence of comorbidities consisting of coronary heart disease, hypertension, and diabetes had been recognized as danger elements for exacerbation of infection.[2]

SARS-CoV-2 belongs to the elegance of enveloped coronavirus and has a genetic collection just like the SARS-CoV-1 (80%) and RaTG-13 coronaviruses (96.2%) discovered in bats.[3] Drug substitute consisting of the usage of off-label capsules is executed presently as an emergency alternative withinside the remedy of SARS-CoV-2 infection. Several capsules used for the remedy of COVID-19 consisting of ribavirin, interferon, favipiravir, lopinavir/ritonavir which have been utilized in SARS or MERS sufferers.[4]

Favipiravir is an anti-influenza drug authorized in Japan and reveals diverse antiviral sports towards RNA viruses. Favipiravir is nicely tolerated in medical trials, even though it is related to a dose-based boom in serum uric acid levels.[5]

Studies at the aspect consequences of favipiravir on its use withinside the remedy of COVID-19 have advanced in view that this drug became installed as one of the healing options. A higher expertise of the rising antiviral aspect consequences of favipiravir in COVID-19 sufferers from latest research is essential in growing and comparing the adoption of powerful remedies for COVID-19. The purpose of this article is to review the safety of using favipiravir for the treatment of the SARS-CoV-2 virus based on the incidence of adverse events in patients diagnosed with COVID-19 and hospitalized.

METHOD

This systematic review includes the original complete article from PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv. We searched for suitable native articles using some specific keywords such as favipiravir, SARS-Cov-2, COVID-19, adverse events, side effects, etc. The studies reviewed were limited to and included people who used English and were published in the last two years.

The selection criteria for research article topics included in this systematic review were adult patients (>18 years) diagnosed with COVID-19 with mild to severe symptoms. This study included patients who were first treated for the diagnosis of COVID-19. This study was conducted from the time the patient was hospitalized until remission or death. Clinical study that included in this review describes studies using favipiravir monotherapy and compares it to other antivirals, placebo, or different times when favipiravir was given. The outcome included is the frequency of side effects in the subjects tested. For case report, we included reports of adverse events that happened during and after treatment of favipiravir.

The conclusions analyzed are the major side effects that occurred in patients based on the studies included and the rare side effects based on case reports of favipiravir use.

Data were extracted using Microsoft Excel which included the author's name, year of publication, research design, and intervention that eligible.

RESULTS

Based on research at PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv, the author found 487 articles. 289 articles were excluded due to inappropriate titles, article types, and summaries. The rest of the article was then analyzed based on the intervention criteria and the suitability of the method and results section for the intended outcome. A total of 12 articles were considered to be satisfied, based on the title, article type, method, and results specified by the author. The study selection flowchart is shown in Figure 1.

A total of 434 patients participated in eight studies, examining the efficacy and observed side effects of favipiravir in the treatment of COVID-19. The study period varies from a minimum of 11 days to a maximum of 8 months. Various study methods were conducted, consisting of randomized and non-

randomized clinical studies, as well as prospective and retrospective cohort studies. The doses of favipiravir in 7 studies show similarities. That is, use 1600 mg each on the first day of treatment and take an additional 600 mg 2–3 times daily until 10–14 days of treatment, but the controls in each study are of different types and cans received.

In case reports, we found four reports of adverse events in 5 patients. Patient side effects were determined both after treatment and during favipiravir treatment according to international guidelines. In three reports, patients were given a starting dose of 3600 mg favipiravir followed by a maintenance dose of 1600 mg, while a report from Atak showed 20 years old patient received an initial dose of 1600 mg followed by 600 mg.[6] Tables 1 and 2 summarize the characteristics of the studies included in this systematic review.

Table 3 shows the side effects reported during administration of favipiravir in each observational study. Three studies reported the incidence of hyperuricemia, four studies reported the incidence of gastrointestinal disorders, the main case of diarrhea, and five studies reported changes in liver enzyme levels. However, in these studies, there was no statistically significant difference in the side effects experienced from favipiravir compared to other antivirals or standard hospital treatments. Chen mentioned in his study the potential for significant hyperuricemia due to favipiravir compared to antiviral arbidol, but overall side effects were not significantly different during the observation period.[4]

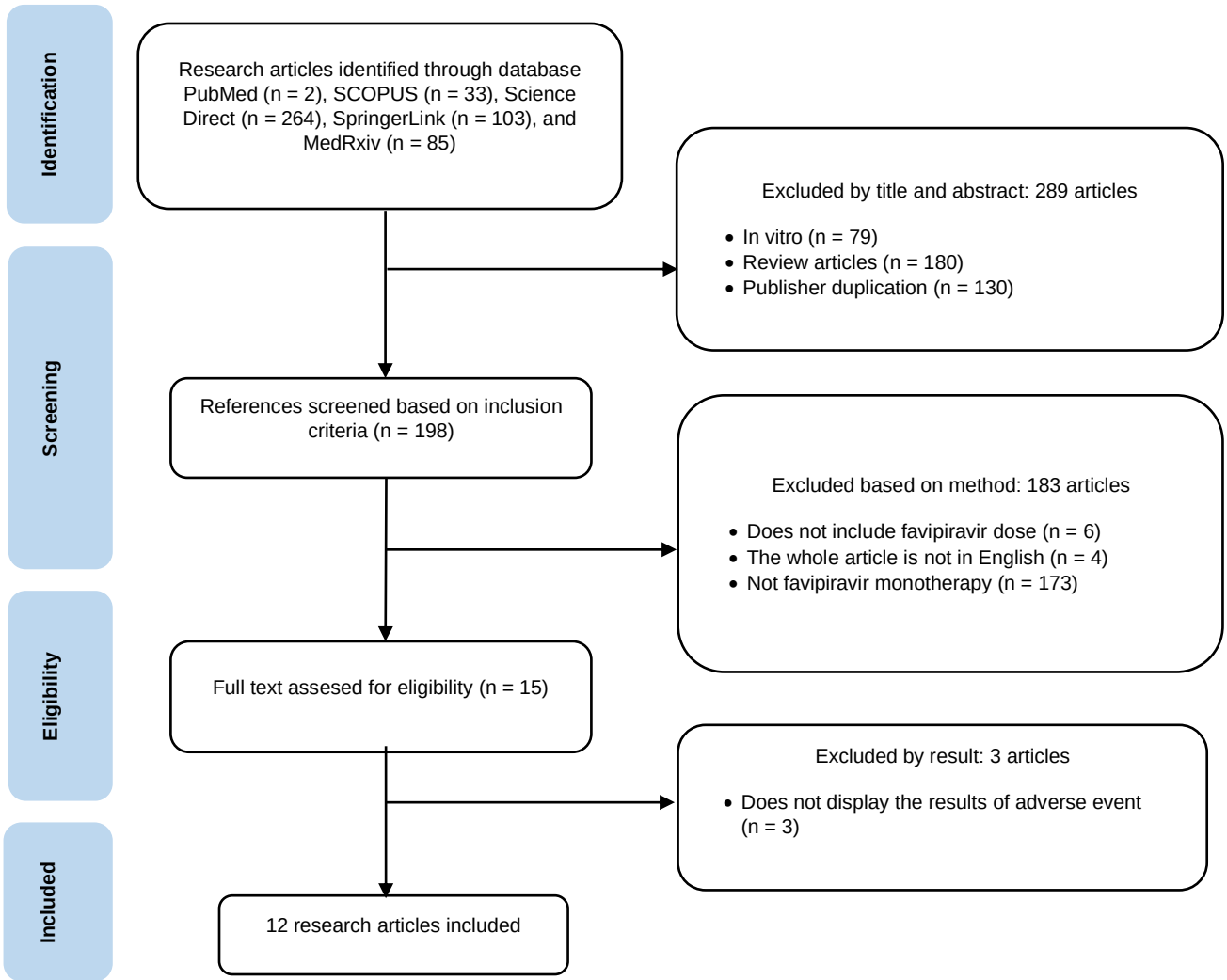


Figure 1. PRISMA flowchart of article selection

Table 1. Summary characteristics of included studies. RCT: randomized control trial, SOC: standard of care

No.	Author, year	Study design	Study duration	Patient criteria	Severity	Favipiravir dose	Number of favipiravir group	Comparator
1.	Lou, 2021[7]	RCT; single center	5 months	Participants confirmed COVID-19.	Not stated	The initial dose is 1600 mg or 2200 mg orally, followed by 600 mg three times a day for a total of 14 days of treatment.	9 participants	(1) baloxavir marboxil group; (2) Control group (Continuing existing antiviral treatment including lopinavir/ritonavir or darunavir/cobicistat and arbidol)
2.	Fujii, 2021[8]	single-center, retrospective cohort study	8 months	Patients with fever, shortness of breath, decreased oxygen saturation, pneumonia on imaging, or worsening respiratory failure.	Severe	1800 mg twice daily on the first day, followed by 800 mg orally twice daily for up to 14 days.	54 participants	SOC
3.	Ivashchenko, 2021[9]	RCT; multicenter	4 weeks	Hospitalized patients with moderate COVID-19 pneumonia	Moderate	1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14, or 1800 mg twice daily on Day 1 and 800 mg twice daily on Days 2–14 (1800/800 mg).	40 participants	SOC
4.	Udwadia, 2021[10]	RCT; multicenter; open-label	7 weeks	Age 18-75 years, mild to moderate COVID-19 infection (including no symptoms).	Mild to moderate	1600 mg twice daily on Days 1 and 600 mg twice daily on Days 2–14.	73 participants	SOC
5.	Cai, 2020[4]	open-label, non-randomized, before-after controlled study	4-week	aged 16–75 years; had no trouble swallowing the pill	Mild to moderate	1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14.	35 participants	Lopinavir/Ritonavir
6.	Dabbous, 2021[11]	multi-center, randomized, interventional study	4 months	SARS-CoV-2 infection with mild or moderate symptoms and hospitalization three days after symptoms start.	Mild to moderate	1600 mg twice daily on day one followed by 600 mg twice daily from day two to ten.	44 participants	Chloroquine
7.	Chen, 2020[12]	prospective, randomized, controlled, open-label multicenter trial	11 days	Positive chest CT scan at the age of 18 years or older; clinical symptoms include fever, cough, shortness of breath, and other signs of lower respiratory tract viral infection.	Moderate, severe, or critical	1600 mg twice daily followed by 600 mg twice daily for 10 days	116 participants	Conventional therapy plus Umifenovir (Arbidol) (200mg three times daily)
8.	Rattanaumpawan, 2020[13]	retrospective observational study	3 months	Patients at least 18 years of age having and receiving at least one dose of favipiravir	Moderate, severe, or critical	1600 mg twice daily on Day 1, followed by 600 mg twice daily on Days 2-10	63 participants	SOC

Table 2. Summary characteristics of the included case report studies.

No.	Author, year	Patient criteria	Favipiravir dose	Occurrence of adverse events
1.	Murai, 2021 [14]	A 64-year-old woman tested positive for COVID-19 and was admitted to the hospital. For about a week, the patient complained of a persistent fever.	3600 mg per day on the first day and 1600 mg per day thereafter	Patient developed a fever (38ºC) on day 12, suspected to be caused by bacterial pneumonia or drug fever. On day 13, favipiravir was stopped. The patient's body temperature gradually decreased after, there was no worsening of symptoms, and her fever was relieved without the use of antimicrobials.
2.	Koshi, 2021 [15]	A 52-year-old lady who tested positive for SARS-CoV-2 had been on maintenance hemodialysis three times a week for three years due to diabetic nephropathy. The patient had a 6-month history of severe diarrhea and had had coronary artery stenting, right lower limb amputation, and latent pulmonary TB therapy.	3600 mg initial dose followed by 1600 mg orally daily in two divided doses	Mild and reversible increase of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP).
3.	Atak, 2021 [6]	A 20-year-old man was hospitalized for COVID-19 infection 16 days ago and was receiving favipiravir	Initial dose 1600 mg twice daily, followed by 600 mg twice daily for 7 days	The patient was readmitted after complaining for two days of a minor itching eruption with a rapid onset. Histology revealed epidermal acanthosis with many neutrophilic subcorneal/intracorneal spongiotic pustules and papillary dermal edema. In the dermis, there was a mixed inflammatory infiltration of lymphocytes, neutrophils, and few eosinophils. The patient has been diagnosed with AGEP caused by favipiravir (Acute generalized exanthematous pustulosis).
4.	Tsuboi, 2021 [16]	FIRST PATIENT: A 70-year-old woman, was a past smoker with co-morbidities such as: emphysema, dyslipidemia, and an overactive bladder. SECOND PATIENT: A 61-year-old woman, has never smoked but suffers from hypertension and dyslipidemia.	Initial dose 3600 mg on the first day and 1600 mg on second day and thereafter.	FIRST PATIENT: decreased of viral load that measured by real-time RT-PCR after treatment, but increased back on day 12, 2 days after the end of treatment. Patient showed transient fever, dyspnea on exertion, a decrease in SpO2 at the same time, but did not worsen thereafter. SECOND PATIENT: RT-PCR examination showed a decrease in viral load during treatment, but transient fever, malaise, dyspnea, and tachypnea on activity also a transient increase in viral load were observed the day after treatment ended.

Table 3. Adverse reactions reported during favipiravir administration in each clinical study. NR: Not reported.

No.	Author, year	Adverse events	Signification
1.	Lou, 2021[7]	Respiratory failure or ARDS (44%); Lymphopenia (77%); Leukopenia (11%); Decreased hemoglobin (77%); Increased aspartate aminotransferase (11%); Increased alanine aminotransferase (44%); Elevated total bilirubin (11%); Albumin decreased (88%); Elevated creatine phosphokinase (11%); Increased lactate dehydrogenase (55%); Increased triglycerides (66%); Improved D-dimmer (55%); Diarrhea (22%); Rash (11%); Nausea (11%)	NR
2.	Fujii, 2021[8]	Hyperuricemia (55.5%), impaired liver function (31.4%), drug eruption (7.4%), drug fever (5.5%), and increased eosinophil count (1.8%)	NR
3.	Ivashchenko, 2021[9]	17.5% of patients experienced side effects in the form of diarrhea, nausea, vomiting, chest pain, and increased levels of liver transaminases.	NR
4.	Udwadia, 2021 [10]	Hyperuricemia (16.4%); Abnormal liver function tests (6.8); Viral pneumonia (2.7%); Gastrointestinal disturbances (1.4%)	NR
5.	Cai, 2020 [4]	Diarrhea (5.71%); liver and kidney injury (2.86%) and others (2.86%)	P<0.001
6.	Dabbous, 2021 [11]	Diarrhea (6.8%); elevated liver enzymes (6.8%); nausea (2.3%); headache (2.3%); anemia (4.5%); hyperuricemia (4.5%); decreased neutrophils (4.5%)	P>0.05
7.	Chen, 2020 [12]	Abnormal LFT (8.62%); Increased serum uric acid (13.79%); Reaction to psychiatric symptoms (4.31%); Gastrointestinal tract reactions (13.79%)	P<0.05 in the incidence of hyperuricemia
8.	Rattanaumpawan, 2020 [13]	Diarrhea (54.0%), followed by nausea/vomiting (7.9%), hepatitis (6.4%) , and QT interval prolongation on the ECG (6.4%). None of these side effects are life-threatening.	NR

DISCUSSION

This systematic review includes publicly available observational studies on the safety of favipiravir use during the COVID-19 pandemic. Favipiravir has dose-dependent side effects and is well tolerated by patients undergoing treatment. The overall safety profile was not significantly different from the comparator products in terms of standard treatment and other antiviral agents.

Favipiravir is associated with the effects of hyperuricemia, such as diarrhea. This is indicated by the percentage that occurred in the observed studies compared to other side effects. Favipiravir is mainly metabolized by aldehyde oxidase, partly metabolized by xanthine oxidase in the liver, and produces favipiravir M1 as an inactive metabolite excreted by the kidneys. The increase in uric acid in the blood caused by favipiravir is due to its action of reducing the amount of uric acid excreted in the urine. Favipiravir and its inactive metabolite M1 are moderate inhibitors of OAT1 and OAT3 (organic anion transporters 1 and 3) that transport uric acid for luminal excretion in the basolateral region. Decreased uric acid uric acid secretion and increased uric acid reuptake via uric acid transporter 1 (uric acid reuptake via uric acid transporter 1) due to inhibition of OAT1 and OAT3 leads to a mechanism of increased blood uric acid.[17]

The dose-dependent effect of favipiravir has been observed in Phase III safety studies. Blood uric acid levels were found to have returned to baseline after discontinuation of treatment. Blood uric acid levels averaged 4.4 mg/dl above baseline 6 days after favipiravir administration (3,200 mg on day 1, followed by 1,200 mg on day 25) and returned to normal 7 days after discontinuation.[17] The incidence of increased blood uric acid (including hyperuricemia) occurred in 9.9% (24/242) of healthy adults in Japan, but was 5.8 in those treated with the recommended dose of favipiravir. It was 5.8% (23 out of 394).[18] This

may also support the results of several observational studies that found that there was no significant difference in blood uric acid levels between patients receiving favipiravir and other antivirals.

The incidence of diarrhea was also mentioned in several studies, but there was no significant difference between favipiravir and comparative antivirals or standard treatments. It is believed that this is because SARS-CoV-2 can also cause diarrhea. The SARS-CoV-2 ACE2 cell receptor is expressed in various types of cells and tissues, including the esophagus, stomach, small intestine, colon, and rectum. The highest gastrointestinal ACE2 expression levels are found in ileal epithelial cells, especially resorbable enterocytes. The direct and indirect effects of cytokines can combine to cause an enterocyte ion imbalance, which can contribute to the development of diarrhea. Viral E-proteins, ionic imbalances, impaired barrier integrity, and dysregulation of the renin vascular tension aldosterone system, which causes inflammation, play important roles in secretory diarrhea and intestinal leakage in patients with COVID-19.[19]

We include 2 cases reported adverse event during therapy with favipiravir such as drug fever, also mild and reversible elevation of liver enzyme. Drug fever is a type of reaction associated with temporary fever caused by drug therapy and disappears when the pathogen is stopped. The main feature that distinguishes drug fever from other causes is the fever that disappears after the drug is stopped. Five mechanisms of drug fever have been identified. Fever can be caused by the effects of drugs on thermoregulation, drug administration-related reactions, pharmacological effects of drugs, idiosyncratic reactions, and hypersensitivity reactions, the most common mechanism of drug fever.

Another 3 cases report showed adverse event after treatment of favipiravir, with 2 cases happened during hospital admission and 1 case after remission. In the two cases reported by Tsuboi et.al, the viral load increase after completion of favipiravir treatment was transient.[16] The viral load spontaneously decreased and the clinical symptoms improved. A slight temporary increase in viral load called "blip" has also been reported during treatment. From this perspective, these two cases may represent phenomena such as "outbreaks" in antiviral treatment. In the case of COVID-19, delays in hospitalization after the onset of the disease have also been reported to prolong SARS-CoV-2 infection.[20] In both cases of this report, antiviral therapy was started relatively late, 10 days after the onset of the disease. This may have caused a phenomenon like "blip".

Koshi et.al reported the first report on the efficacy of favipiravir in end- stage renal disease (ESRD) patients undergoing hemodialysis.[15] It showed that favipiravir may be an effective option for treating patients with ESRD infected with COVID-19 based on improvement in vital sign and laboratory data, with mild and reversible elevation of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP). Despite this finding, the safety of Favipiravir in COVID-19 patients with or without concurrent renal problems requires further data and a more comprehensive analysis.

The studies included in this review are limited. This work was limited to the environment and population contained in the research center with adult participants. As a result, the results are less applicable to younger patients with COVID-19. No conclusions can be drawn from the 12 studies due to the different study designs that involve the discussion of case reports. Case reports are for support purposes only.

The authors are grateful to the Directorate of Research and Development, Universitas Indonesia, for their financial support through PUTI Q1 Grant No. NKB-1274/UN2.RST/HKP.05.00/2020.

CONCLUSIONS

Based on clinical study, the use of favipiravir to treat COVID-19 causes several adverse events such as diarrhea, changes in liver enzymes, and increased uric acid. Some are less important than other antiviruses and reversible. In case reports, there are rare adverse event such as acute generalized

exanthematous pustulosis (AGEP), we also include transient increase in viral load the day after treatment favipiravir ended.

To improve the efficacy and safety of COVID-19 therapy, it is important to develop incident reports of antiviral side effects in special populations such as children, pregnant women, and organ dysfunction. If favipiravir is considered prophylactic, further studies of the long-term effects of treatment are needed.

REFERENCES

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med. 2020;382(13):1199–207.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
3. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ. 2020;371:1–6.
4. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020;6(10):1192–8.
5. Łagocka R, Dziedziejko V, Kłos P, Pawlik A. Clinical Medicine Favipiravir in Therapy of Viral Infections. J Clin Med. 2021;10:273.
6. Atak M, Farabi B, Akbayrak A, Kalelioğlu M, Rao B. Acute generalized exanthematous pustulosis following treatment with favipiravir in a patient with COVID-19 without hydroxychloroquine use: Report of the first case. J Cosmet Dermatol. 2021;20(8):2387–9.
7. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. Eur J Pharm Sci. 2021;157:105631.
8. Fujii S, Ibe Y, Ishigo T, Inamura H, Kunimoto Y, Fujiya Y, et al. Early favipiravir treatment was associated with early defervescence in non-severe COVID-19 patients. J Infect Chemother. 2021;27(7):1051–7.
9. Ivashchenko AA, Dmitriev KA, Vostokova N V, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for Treatment of Patients With Moderate Coronavirus Disease 2019 (COVID-19): Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. Clin Infect Dis. 2021;73(3):531–4.
10. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis. 2021;103:62–71.
11. Dabbous HM, Abd-Elsalam S, El-Sayed MH, Sherief AF, Ebeid FFS, El Ghafar MSA, et al. Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. Arch Virol 2021 1663. 2021;166(3):949–54.
12. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. 2020;
13. Rattanaumpawan P, Road W. Real-world Experience with Favipiravir for Treatment of COVID-19 in Thailand: Results from a Multicenter Observational Study. 2020;
14. Murai Y, Kawasuji H, Takegoshi Y, Kaneda M, Kimoto K, Ueno A, et al. A case of COVID-19 diagnosed with favipiravir-induced drug fever based on a positive drug-induced lymphocyte stimulation test. Int J Infect Dis. 2021;106:33–5.
15. Koshi E, Saito S, Okazaki M, Toyama Y, Ishimoto T, Kosugi · Tomoki, et al. Efficacy of favipiravir for an end stage renal disease patient on maintenance hemodialysis infected with novel coronavirus disease 2019. CEN Case Rep. 2021;10(1):126–31.
16. Tsuboi H, Kasamatsu Y, Matsubara S, Sasao A, Kunimitsu K, Munakata N, et al. Two cases of novel coronavirus infection (COVID-19) with

transient viral elevation using semi-quantitative real-time reverse transcription PCR and symptom relapse after completion of 10 days of favipiravir treatment. J Infect Chemother. 2021;27(7):1072–5.

17. Mishima E, Anzai N, Miyazaki M, Abe T. Uric Acid Elevation by Favipiravir, an Antiviral Drug. Tohoku J Exp Med. 2020;251(2):87–90.
18. Evaluation and Licensing Division - Pharmaceutical and Food Safety Bureau - Ministry of Health - Labour and Welfare. Report on the Deliberation Results: Avigan Tablet 200 mg. Tokyo; 2014.
19. Megyeri K, Dernovics Á, Al-Luhaibi ZII, Rosztóczy A. COVID-19-associated diarrhea. World J Gastroenterol. 2021;27(23):3208.
20. Xu K, Chen Y, Yuan J, Yi P, Ding C, Wu W, et al. Factors Associated With Prolonged Viral RNA Shedding in Patients with Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2020;71(15):799–806.

The Efficacy of Remdesivir in Reducing SARS-CoV-2 Viral Load and Its Safety on COVID-19 Patients: A Systematic Review

Afifah Fauziyyah, Ratika Rahmasari, Rani Sauriasari

Faculty of Pharmacy, Universitas Indonesia, Depok

Abstract

Background: *This study aimed to examine the effectiveness of Remdesivir in reducing Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) viral load and its safety for antiviral therapy in Coronavirus disease 2019 (COVID-19) treatment.*

Methods: *This systematic review used data sources from the PubMed, ProQuest, SpringerLink, and ClinicalTrial.gov databases for relevant observational and interventional studies during August 2020 to August 2021. Studies evaluating Remdesivir in adults hospitalized for COVID-19 were included in this review. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.*

Results *This review found 9 studies that were relevant to the study objectives. In total, 1,088 patients participated as subjects. Three studies demonstrated the effect of remdesivir in reducing SARS-CoV-2 viral load in upper and lower respiratory tract specimens. Six studies demonstrated that remdesivir was safe for use in a variety of baseline conditions (patients on hemodialysis and patients receiving kidney transplantation), had no significant hepatotoxicity, did not increase the risk of acute kidney injury, and did not increase eGFR or systemic symptoms in patients taking remdesivir.*

Conclusion: *Remdesivir has been shown to reduce SARS-CoV-2 viral load and was safe for use as antiviral therapy in the treatment of COVID-19, but an assessment of randomized controlled trial for the effect of Remdesivir on viral load reduction was not available yet.* ***(J Respirol Indones 2022; 42(1): 76-85)***

Keywords: *COVID-19, remdesivir, SARS-CoV-2 viral load, safety, systematic review*

Pengaruh Remdesivir dalam Menurunkan *Viral Load* SARS-CoV-2 dan Keamanannya pada Pasien COVID-19: Tinjauan Sistematis

Abstrak

Latar belakang: *Penelitian ini bertujuan menilai efektivitas remdesivir terhadap penurunan* viral load dari Severe Acute Respiratory Syndrome Coronavirus 2 *(SARS-CoV-2) dan keamanannya sebagai terapi antivirus pada pengobatan* Coronavirus disease *2019 (COVID-19).*

Metode: *Tinjauan sistematis ini menggunakan data yang bersumber dari pangkalan data* Pubmed, ProQuest, SpringerLink, *dan* ClinicalTrial.gov *untuk uji observasional dan intervensional yang relevan selama Agustus 2020 hingga Agustus 2021. Penelitian yang mengevaluasi remdesivir pada pasien dewasa yang dirawat di rumah sakit karena COVID- 19 diikutkan dalam tinjauan ini. Tinjauan sistematis ini mengikuti panduan penulisan* Preferred Reporting Items for Systematic Reviews and Meta-analyses *(PRISMA).*

Hasil: *Ada 9 penelitian yang relevan dengan tujuan penelitian ditemukan. Total terdapat 1.088 pasien yang turut serta sebagai subjek penelitian. Tiga penelitian menunjukkan efek remdesivir dalam menurunkan* viral load *SARS-CoV-2 pada spesimen saluran pernapasan atas dan bawah. Enam penelitian membuktikan remdesivir aman digunakan pada berbagai kondisi dasar (pasien dalam hemodialisis dan pasien penerima transplantasi ginjal), tidak memiliki hepatotoksisitas yang bermakna, tidak meningkatkan risiko* acute kidney injury*, dan tidak meningkatkan eGFR atau gejala sistemik pada pasien yang menggunakan remdesivir.*

Kesimpulan: *Remdesivir telah terbukti menurunkan* viral load *SARS-CoV-2 dan aman digunakan sebagai terapi antivirus pada pengobatan COVID-19, namun belum ada penilaian dari uji acak terkontrol mengenai efek remdesivir terhadap penurunan* viral load*.* ***(J Respirol Indones 2022; 42(1): 79-85)***

Kata Kunci: *COVID-19, remdesivir,* viral load *SARS-CoV-2, keamanan, tinjauan sistematis*

Correspondence: Rani Sauriasari
Email: rani@farmasi.ui.ac.id

INTRODUCTION

Since the emergence of COVID-19 as a worldwide outbreak, the World Health Organization (WHO) issued an emergency use authorization (EUA) regarding antiviral therapy which could be used in this condition. One of the antivirus was remdesivir (RDV).[1]

Remdesivir (also known as GS-5734) is a nucleoside analogue which acts by inhibiting RNA-dependent RNA polymerase that has previously been used to treat SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) which are structurally similar to COVID-19.[2]

To find out the increase in COVID-19 cases, measuring the viral load is one of the strategies. Viral load quantification is very useful for evaluating severity of infection, predicting the evolution of viral infection and its recurrence.[3]

In an in vitro study, RDV was able to inhibit the SARS-CoV-2 replication.[4] Research conducted on Vero E6 Cells showed that RDV was able to reduce infectious viruses (EC_{50} = 23.15μM) and to reduce viral RNA copies ((EC_{50} = 26.90 μM).[5] Treatment of RDV in a Ces1c-/- hDPP4 mouse model infected with MERS-CoV was found to decrease the viral load.[6]

A study conducted on rhesus macaques demonstrated that RDV reduced viral titration in bronchoalveolar lavage after 12 hours from the first administration of RDV, and reduced pulmonary viral load after 7 days of therapy. This study also demonstrated that lung damage in animals receiving RDV therapy was reduced, and supported an early initiation of RDV treatment in COVID-19 patients to prevent pneumonia.[7,8]

In this systematic review we reviewed recent sources to determine the effectiveness of using RDV with SARS-CoV-2 viral load measurement. Given that there is no gold standard yet in the COVID-19 treatment, and RDV is still categorized as EUA by WHO, it is necessary to conduct a new study on the safety of using RDV.

METHOD

Search Strategy

Reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.[9] Literature searches were carried out systematically through the ProQuest, PubMed, SpingerLink, and ClinicalTrials.gov databases.

The literature search strategy is detailed in e-Tables 1, 2, and 3 on the Supplementary data. The research publication year was limited from August 2020 to August 2021. the search for literature sources was not limited to English.

Literature screening was conducted independently by AF and RR. First, we identified the duplicated literature and excluded them. Once there were no duplicated literatures, title and/or abstract screening was performed. Titles and/or abstracts which were not relevant to the desired result; and not RCT, Cohort, or Case-control studies were excluded. Furthermore, the full text of the study would be reviewed and selected for qualitative analysis. Disagreements among investigators would be resolved by consensus, and if necessary, consultation with a third investigator (RS).

Inclusion criteria

Observational and interventional studies included were studies that discussed the effectiveness of RDV by measurement of SARS-CoV-2 viral load and/or safety of RDV therapy compared with other antiviral therapies, placebo, or standard of care (SoC) therapies for COVID-19. The criteria for positive COVID-19 patients were evidenced by the RT-PCR results, were hospitalized, and were≥18 years old.

Exclusion criteria

The exclusion criteria were duplicate studies, review articles, meeting abstracts, case reports, case series, letters and editorials, brief communication, in vitro and in vivo studies, and studies without original information on RDV therapy.

Data extraction

Data on the author's name, study design, number of patients, duration of illness before RDV use, inclusion criteria, groups or subgroups of patients, viral load measurements and safety were extracted.

Risk of bias assessment

We used the Newcastle-Ottawa Scale[10] to assess the risk of bias in observational study. The researchers independently assessed the risk of bias with the tool, and then other researchers re-examined them.

RESULTS

From 1478 studies identified through database searches (ProQuest: 648; PubMed: 370; SpringerLink: 452; ClinicalTrial.gov: 8), about 22 full-text articles were selected. After matching our eligibility criteria, 9 relevant observational studies were included in this review for qualitative analysis (Figure 1). Complete data from the qualitatively analyzed studies are shown in Table 1.

Viral Load

Measurement of the SARS-CoV-2 viral load in 86 patients in South Korea was performed at three-time points, namely between days 1–5, between days 6-10, and between days 11–15 of hospital admission (HA). It used the upper and lower respiratory tract specimens. To measure viral load reduction, changes in C_T value of the RNA-dependent RNA polymerase gene were evaluated on day 15 of hospital admission in both groups (RDV vs. SoC). Analysis of upper respiratory tract specimens in the RDV group showed significantly higher C_T values (n=46; median=1.33; interquartile range [IQR]=0.62-1.33) compared to the SoC group (n=35; median=0.80; IQR=0.19-1.13; *P*=0.043).[11]

On the lower respiratory tract analysis, the RDV group also showed a higher increase in C_T values (n=33; median=0.99; IQR=0.26-1.15) compared to the SoC group (n=28; median=0.75; IQR= -0.05 - 0.99) but the difference was not significant (*P*=0.291).[11] Evaluation of viral load reduction using RT-PCR-tested upper respiratory tract specimens at each time point (HA 1-5, 6-10, and 11-15) were selected and compared. Slope C_T values were significantly higher in the RDV group (mean, 5.10±3.08) than in the SoC group (mean, 2.68±3.63; *P* = 0.007).

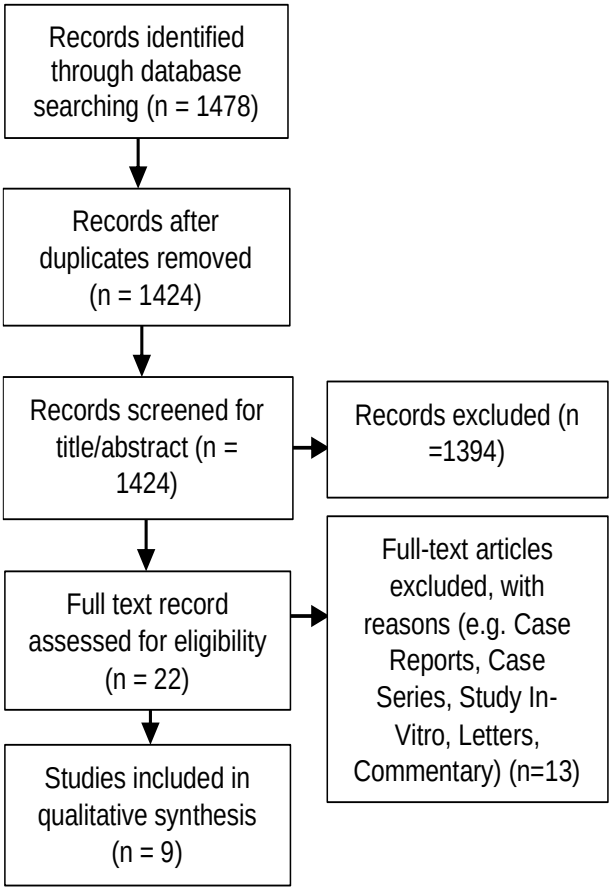


Figure 1. Flow Chart of PRISMA

The increase in C_T values from HA 1-5 to 11–15 was also significantly higher in the RDV group (n=32; mean=10.19±6.16) than the SoC group (n=28; mean=5.36±7.27; *P*=0.007).[11]

Results on lower respiratory tract specimens pointed that the slope of the increase in C_T values was higher in the RDV group (n=21; mean=4.54±3.93) than in the SoC group (n=21; mean=2.97±3.36), but not statistically significant (*P*=0.170). The RDV group demonstrated a higher increase in C_T values from HA days 1-5 to days 11-15 (mean, 9.02±7.84) compared to the SoC group (mean, 5.94±6.72), but the difference was not significant (*P*=0.179).[11]

Table 1. The study design and the measured outcome of the included studies

Authors (years)	Type of Study	Selected details of study design and participants	Group 1 sample size	Group 2 sample size	Median duration of illness before RDV therapy	Outcome
VIRAL LOAD						
Joo, et al. (2021)	Cohort study	Severe Illness Group 1: RDV Group Group 2: Supportive care group	48	38	7.42 days	Slope of C_T values (P = 0.043); median (IQR): - RDV= 1.33 (0.62–1.33) - Supportive care= 0.80 (0.19–1.13) Difference in changes of C_T values from days 1–5 to days 11–15 (P = 0.007); mean: - RDV= 10.19±6.16 - Supportive care= 5.36±7.27
Goldberg, et al. (2021)	Observational study	Severe COVID-19 Group 1: RDV Group 2: Control	29	113	Not mentioned	a. First point to end point, decrease (%) (P=0.7349): RDV: 13.8% Control: 11.5% b. First point to mid-point (P=0.1120) RDV: 31% Control: 17.7% c. Mid-point to end point (P=0.588): RDV: 24.1%, Control: 29.2%
Barratt-Due, et al. (2021)	Clinical study	Group 1: RDV + SoC Group 2: SoC	42	57	7.4 days	Viral load, Log10 count/1000 cells (SD): Group 1: 1.6 (1.6) Group 2 2: 2.3 (1.8) Measurements were carried out on days 3–5, 7–9, and then every 3 days
SAFETY						
Aiswarya, et al. (2021)	Observational, prospective study	Moderate or severe illness -	48	-	3 days (IQR, 2-4 days)	1. Acute coronary syndrome = 1 patient 2. Worsening of behavioral disorder = 1 patient
Kalligeros, et al. (2020)	Phase 3, Clinical trial	Group 1: RDV Group 2: Supportive care	99	125	6 days (IQR, 3-8 days)	1. AKI; patients (%) - stage 1: 14 (54) - stage 3: 12 (46) 2. AST increase; patients (%) - Grade 1: 35(100) 3. ALT increase; patients (%) - Grade 1: 31(100) 4. Serum total bilirubin increase; patients (%) - Grade 1: 8(50) - Grade 2: 5 (31) - Grade 3:3 (19)
Buxeda, et al. (2021)	Cohort study	-	51	-	3 days (IQR, 2–5 days)	1. AKI: 11.7% 2. T-cell mediated rejection: 1 patient 3. Another patient presented thrombotic microangiopathy

Authors (years)	Type of Study	Selected details of study design and participants	Group 1 sample size	Group 2 sample size	Median duration of illness before RDV therapy	Outcome
Falcão, et al. (2021)	Cohort study	Group 1: Hydroxychloroquine Group 2: RDV	101	48	Not mentioned	Hepatobiliary disorders; patients (%): 4 (8.3%) Acute renal failure:1 (2.1%) Nervous system disorders: 1 (2.1%) Other disorders: 1 (2.1%)
Garcia-Vidal, et al. (2021)	Cohort study	Group 1: RDV Group 2: Control	123	119	7 days (4–9 IQR)	No adverse events requiring remdesivir discontinuation were reported
Biancalana, et al. (2021)	Observational, retrospective study	Group 1: RDV Group 2: Control	80	29	Not mentioned	Very small percentage developed AKI

An Israeli study involving 142 patients comparing viral load reductions in the RDV vs control group found that the viral load measurement decreased by 13.8% vs 11.5% (*P*=0.7349) from the first point to the last point; 31% vs 17.7% (*P*=0.112) from the first point to midpoint; and 24.1% vs 29.2% (*P*=0.588) from midpoint to the endpoint. Patients receiving RDV therapy were found to have slightly lower viral loads than those not receiving this therapy in the first trial, although the difference was not significant (26.8±7.05 vs 25.67±6.02, *P*=0.36). This difference remained insignificant when the final tests of the two groups were compared (33.94±5.22 vs 32.54±5.78, *P*=0.109).[12]

Early administration of RDV (< first 7 days after symptom onset) could significantly increase clinical improvement. The study showed that within a median of 11 days after symptom onset and receiving RDV therapy, 37 of 196 (19%) patients no longer had detectable viral RNA on nasopharyngeal and oropharynx swabs.[13,18]

A study using oropharyngeal swab specimens showed viral load measurements of log10/1000 cells (SD) in the RDV group and the SoC group of 1.6 (1.6) vs 2.3 (1.8). The viral load measurements between the two groups were not significantly different but the group of patients taking RDV generated lower measurements results.[13]

Safety

A study conducted on 48 dialysis patients found that the use of RDV in COVID-19 patients had no immediate adverse effects. One patient experienced acute coronary syndrome, 6 hours after the first dose of RDV. One patient experienced worsening behavior after 15 hours of RDV use. Patients >50 years old had a significant decrease in serum ferritin (*P* = 0.005). Six patients with elevated serum ALT levels at admission were not observed to have worsened due to RDV therapy (*P* = 0.35).[14] In this study, there was no control group, so adverse events were only explained based on findings without comparison, which was a source of bias in this study (Table 2).

Another cohort study with 99 subjects taking RDV obtained that there were 14 subjects with stage 1 acute kidney injury (AKI) and 12 subjects with stage 3 AKI.

There were 35 subjects who had elevated aspartate aminotransferase (AST) grade 1 and 31 subjects experienced increase in alanine aminotransferase (ALT). The increase in total serum bilirubin grade 1 was experienced by 8 patients, 5 patients in grade 2, and 3 patients in grade 3. The incidence of AKI, transaminitis, and hyperbilirubinemia occurred in the RDV group and the supportive care group was not significantly different (AKI, *P*=0.12; increased AST, *P*=0.20; increased ALT, *P*=0.25; increase in total serum bilirubin, *P*=0.94).[15]

A study of 51 kidney transplant recipients who used RDV as COVID-19 treatment found that AKI occurred in 27.7% of patients. Most were stage 1 AKI (57.1%) and only 1% required renal replacement

therapy (RRT). Of the 14 recipients who had AKI, increase in SCr prior to the initiation of RDV was demonstrated by 8 recipients, therefore, renal dysfunction could not be attributed to drug use. AKI after RDV initiation occurred in 11.7% of subjects. No subject required discontinuation of RDV therapy due to renal impairment. RDV was well tolerated, so there were no significant safety concerns with drug administration.[16]

The study included 48 subjects taking RDV known to have comorbid diseases (cardiovascular disease, asthma, pulmonary disease, cancer, liver disease, kidney disease, diabetes and HIV). In this study 102 adverse drug reactions (ADRs) were identified. The mean time to ADR was 3.9 days, with onset from day 2 and day 7. Hepatobiliary disorders were identified in RDV therapy, as identified in 4 (8.3%) subjects, while acute renal failure was identified in 1 (2.1%) subject, nervous system disorders occurred in 1 (2.1%) subject, and other disorders occurred in 1 (2.1%) subject. The incidence of ADR was significantly higher (47.5%) in hydroxychloroquine (as the comparison group in this study) than in RDV (12.5%) (P<0.001).[17]

A study conducted in Spain with 123 subjects stated that RDV was used in four subjects with chronic kidney disease and 24 subjects with reduced immunity (13 with solid neoplasms, 8 with hematological disease and 3 with HIV infection). Median baseline creatinine (IQR) was 0.86 mg/dL (0.72–1.08); but 6 subjects had creatinine values >1.5 mg/dL (1.52 to 1.75 mg/dL) when the RDV was used.

All patients were discharged with creatinine values <1.40 mg/dL (0.84 to 1.40 mg/dL). One subject with an initial creatinine value of 1.39 mg/dL, was discharged with a value of 1.72 mg/dL. Median values (IQR) of initial AST and ALT (before starting RDV) were 39 (24–64) U/L and 36 (23–61) U/L, respectively, while the median values at discharge were 33 (19–57) U/L and 60 (35–97) U/L. The median (IQR) lymphocyte count at baseline and at discharge were 1 (0.8–1.3) x10^9/L and 1.7 (1.2–2.2) x10^9/L, respectively.

No adverse events requiring discontinuation of RDV were reported in this study.[18]

Table *2*. Risk of bias assessment with Newcastle-Ottawa scale

Author (years)	Selection				Comparability	Outcome			Total
	Representativeness	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration		Assessment of Outcome	Follow-up	Adequacy of Follow-up	
Joo, et al. (2021)	B*	A*	A*	A*	A*	B*	A*	A*	8
Goldberg, et al. (2021)	B*	A*	A*	A*	A*	B*	A*	B*	8
Barratt-Due, et al. (2021)	A*	A*	A*	A*	A*	A*	A*	B*	8
Aiswarya, et al. (2021)	A*	NA	A*	A*	NA	D	A*	B*	5
Kalligeros, et al. (2020)	B*	A*	A*	A*	A*	D	A*	A*	7
Buxeda, et al. (2021)	A*	A*	A*	A*	A*	A*	A*	A*	8
Falcão, et al. (2021)	B*	C	A*	A*	B*	B*	A*	A*	7
Garcia-Vidal, et al. (2021)	A*	A*	A*	A*	A*	B*	A*	A*	8
Biancalana, et al. (2021)	B*	A*	A*	A*	A*	B*	A*	A*	8

Note: NA=Not Available. A, B, C, D are the answers to each question of the Newcastle-Ottawa scale. A star (*) is given to answer A and B. The Stars are count to produce a total score. In general, a study with greater total score has lesser risk of bias.

A study of 80 subjects taking the RDV found that the estimated glomerular filtration rate (eGFR) in the living patients was 81.0±7.4 and the eGFR in deceased patients was 87.8±6. Clinical use of RDV is associated with increased eGFR. In elderly patients who died, the decline in renal function at hospital admission was inversely related to the value of C-reactive protein (CRP). CRP is the most widely used indicator of inflammation to predict disease severity in COVID-19 patients. This confirms the possibility of impaired renal function due to systemic inflammation or due to more severe viral infection.[19]

DISCUSSION

Remdesivir: an introduction

RDV is a broad-spectrum antiviral that exhibits antiviral activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2.[20] RDV is administered intravenously in a single dose of 200 mg on the first day. A dose of 100 mg every 24 hours is given from the second day to 5 or 10 days.[21,22] This drug is a prodrug with molecular formula C27H35N6O8P and an exact mass of 602.23 Da. In the body, RDV is converted into an active molecule known as GS-441524, with the molecular formula C12H13N5O4 (291.10 Da).[23] The effectiveness and safety of RDV for COVID-19 have not been established. On May 1, 2020, the US Food and Drug Administration (USFDA) issued an EUA for the use of RDV as the treatment of hospitalized severe COVID-19 patients.[24]

Remdesivir and SARS-CoV-2 viral load

In a study conducted in New York, it was observed that viral load was associated with the duration and severity of symptoms.[25] Viral load and mortality had a significant correlation.[26] Severity of respiratory disease, increased markers of inflammation, increased risk of death, and lower absolute lymphocyte counts were associated with higher viral load.[27] Decreased lymphocytes were known to indicate a risk of developing more severe disease.[28]

The decrease in viral load was also associated with timing of the first administration of RDV. It is known that the spread of SARS-CoV-2 from the respiratory tract reaches its peak on day 2–3 from the onset of clinical symptoms. Early administration of drugs could shorten the length of stay in the hospital, lower the need for mechanical ventilation, and the results of nasopharyngeal and oropharyngeal swabs could also be less detectable.[18]

Studies have shown that RDV was effective in reducing the viral load of SARS-CoV-2. This may be related to its mechanism of action as a nucleoside analogue under research which acts as a competitive inhibitor of viral RNA-dependent RNA polymerase (RdRp).[29] The reduction in SARS-CoV-2 viral load in the tested patients was also accompanied by lower mortality, clinical improvement, shorter hospital stays, and lower intubation rates, which are in agreement with the previously described theory.[12] Patients requiring mechanical ventilation prior to day 28 of hospitalization were less and the duration of mechanical ventilation was shorter in patients using RDV.[11] These findings supported the clinical efficacy of RDV treatment for COVID-19 patients.

Safety of remdesivir

Side effects of RDV can be divided into hepatotoxicity, gastrointestinal symptoms, respiratory toxicity, cardiovascular toxicity, nephrotoxicity, and reproductive toxicity.[30] The most common side effects are diarrhea, rash, AKI, hypotension, anorexia, nausea, vomiting, elevated aminotransferases or bilirubin, and worsening cardiopulmonary status.[31,32]

A review of 6 studies showed that the use of RDV caused acute coronary syndrome and behavioral deterioration.[14] The use of RDV also caused AKI, elevated AST and ALT, and elevated total serum bilirubin, but there were no significant differences between RDV and supportive care groups. Thus, it could not be concluded that the incident was due to RDV.[15] T-cell mediated rejection and thrombotic microangiopathy were also known to occur with RDV.[16]

Hepatobiliary disorders, acute renal failure, and nervous system disorders had also been reported in the studies we reviewed. Overall, the side

effects that occurred in patients taking RDV were not significantly different from the control group, supportive care, placebo or other therapies used as comparison.[19]

Patients who took the RDV >48 hours from admission showed longer time to discharge (12.5 vs 22.5 days from admission), which suggested that earlier treatment might be associated with better clinical outcomes.[16] From the various studies reviewed in this study it was obtained that RDV did not worsen renal function in elderly individuals with and without CKD. Some patients demonstrated a relevant increase in eGFR during RDV administration, this trend seemed to be related to the possibility of recovery from SARS CoV-2 and a better prognosis.[19]

This review found no RCTs. There have been few studies on the effectiveness of remdesivir in reducing viral load and none using an RCT design. The abstract of this paper was presented at the 16th APRU Multi-Hazards Symposium 2021 organized by Disaster Risk Reduction Center Universitas Indonesia in collaboration with Association of Pacific Rim Universities.

CONCLUSION

Remdesivir was effective in reducing viral load, although in some studies there were no significant reductions between remdesivir and control groups. The therapeutic efficacy of remdesivir could be determined by the reduction of SARS-CoV-2 viral load. In addition, information on the reduction in the SARS-CoV-2 viral load could be used to determine the extent of its spread. Remdesivir has been proven safe for COVID-19 therapy because it did not worsen CKD, did not cause AKI, did not increase the level of AST, ALT, and total serum bilirubin, and did not exhibit gastrointestinal disturbances, rash, and hypotension in patients. The safety of remdesivir therapy should be monitored as long as the gold standard for COVID-19 therapy has not been established.

Co-authors: Anna rozaliyani, Anom bowolaksono, Muhareva raekiansyah, Muhammad alkaff also provided information related to the ideas in writing this article.

REFERENCES

1. Gilead Sciences. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Veklury (Remdesivir). 2020. p. 1–35.
2. Lukito JI. Tinjauan Antivirus untuk Terapi COVID-19. 340 Cdk-286. 2020;47(5):PP:342.
3. Cuenca-Pardo J, Ramos-Gallardo G, Vélez-Benítez E, Álvarez-Díaz C de J, Bucio-Duarte J, Iribarren-Moreno R, et al. The importance of reducing the viral load to diminish the risk of COVID-19 spread. Cirugía Plástica. 2020;30(2):78–93.
4. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.
5. Choy K, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KPY, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020;178.
6. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1).
7. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020;117(12):6771–6.
8. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature. 2020;585(7824):273–6.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA

2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372.

10. Stang A. scale Critical evaluation of the Newcastle-Ottawa for the assessment of the quality of nonrandomized studies in meta-analyses. 2014;25(9):603–5.
11. Joo EJ, Ko JH, Kim SE, Kang SJ, Baek JH, Heo EY, et al. Clinical and Virologic Effectiveness of Remdesivir Treatment for Severe Coronavirus Disease 2019 (COVID-19) in Korea: a Nationwide Multicenter Retrospective Cohort Study. J Korean Med Sci. 2021;36(11):1–13.
12. Goldberg E, Ben Zvi H, Sheena L, Sofer S, Krause I, Sklan EH, et al. A real-life setting evaluation of the effect of remdesivir on viral load in COVID-19 patients admitted to a large tertiary centre in Israel. Clin Microbiol Infect. 2021;27(6):917.e1-917.e4.
13. Barratt-Due A, Olsen IC, Nezvalova-Henriksen K, Kåsine T, Lund-Johansen F, Hoel H, et al. Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19. Ann Intern Med. 2021;174(9):1261–9.
14. Aiswarya D, Arumugam V, Dineshkumar T, Gopalakrishnan N, Lamech TM, Nithya G, et al. Use of Remdesivir in Patients With COVID-19 on Hemodialysis: A Study of Safety and Tolerance. Kidney Int Reports. 2021;6(3):586–93.
15. Kalligeros M, Tashima KT, Mylona EK, Rybak N, Flanigan TP, Farmakiotis D, et al. Remdesivir Use Compared With Supportive Care in Hospitalized Patients With Severe COVID-19: A Single-Center Experience. Open Forum Infect Dis. 2020;7(10):1–8.
16. Buxeda A, Arias-Cabrales C, Pérez-Sáez MJ, Cacho J, Cabello Pelegrin S, Melilli E, et al. Use and Safety of Remdesivir in Kidney Transplant Recipients With COVID-19. Kidney Int Reports. 2021;6(9):2305–15.
17. Falcão F, Viegas E, Carmo I, Soares J, Falcao M, Solano M, et al. A prospective, observational study to evaluate adverse drug reactions in patients with COVID-19 treated with remdesivir or hydroxychloroquine: A preliminary report. Eur J Hosp Pharm. 2021;28(5):248–53.
18. Garcia-Vidal C, Meira F, Cózar-Llistó A, Dueñas G, Puerta-Alcalde P, Garcia-Pouton N, et al. Real-life use of remdesivir in hospitalized patients with COVID-19. Rev Esp Quimioter. 2021;34(2):136–40.
19. Biancalana E, Chiriacò M, Sciarrone P, Mengozzi A, Mechelli S, Taddei S, et al. Remdesivir, renal function and short-term clinical outcomes in elderly covid-19 pneumonia patients: A single-centre study. Clin Interv Aging. 2021;16:1037–46.
20. Montastruc F, Thuriot S, Durrieu G. Hepatic Disorders With the Use of Remdesivir for Coronavirus 2019. Clin Gastroenterol Hepatol. 2020;18(12):2835–6.
21. Adhikari S, Khadka S, Dahal S, Shrestha DB, Shahi J, Bajgain Y. Remdesivir in COVID-19 management: availability and relevance to low- and middle-income countries. Drugs Ther Perspect. 2021;37(1):26–8.
22. Sun D. Remdesivir for treatment of COVID-19: Combination of pulmonary and IV administration may offer aditional benefit. AAPS J. 2020;22(4):77.
23. Frediansyah A, Nainu F, Dhama K, Mudatsir M, Harapan H. Remdesivir and its antiviral activity against COVID-19: A systematic review. Clin Epidemiol Glob Heal. 2021;9:123–7.
24. ASHP. Assessment of Evidence for COVID-19-Related Treatments : Updated 01 / 29 / 2021. 2021. 1–155 p.
25. Argyropoulos K V., Serrano A, Hu J, Black M, Feng X, Shen G, et al. Association of Initial Viral Load in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Patients with Outcome and Symptoms. Am J Pathol. 2020;190(9):1881–7.
26. Pujadas E, Chaudhry F, McBride R, Richter F, Zhao S, Wajnberg A, et al. SARS-CoV-2 viral load predicts COVID-19 mortality. Lancet Respir Med. 2020;8(9):e70.
27. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS-CoV-2 viral load is

associated with increased disease severity and mortality. Nat Commun. 2020;11(1):1–9.

28. Raharjo AM, Sari ED, Mufida DC. Correlation Between Leukocyte Differential Counts with The Severity and Outcome of Coronavirus Disease 2019 (Covid-19) Patients in Jember. J Respirologi Indones. 2021;41(3):187–95.
29. Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3.
30. qianqian fan bo zhang, Jie M, Shuyang Z. Safety profile of the antiviral drug remdesivir: An update. Biomed Pharmacother. 2020;130:1–3.
31. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–78.
32. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020;382(24):2327–36.

AUTHORS INDEX

SUBJECTS INDEX