Original Article

Proportions of Hypertension in Stable COPD Patients at the National Respiratory Center Persahabatan Hospital

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Most of these deaths are related to cardiovascular disease. This is due to systemic inflammation that causes increased vascular stiffness and hypertension. These comorbidities lead to poor quality of life, low exercise tolerance, and an increased risk of hospitalization. This study aims to report the proportion of hypertension among stable COPD patients in the Indonesian population.

Methods: This cross-sectional study was conducted at the National Respiratory Center Persahabatan Hospital between February and March 2023. Stable COPD patients admitted to the Asthma and COPD Polyclinic who met the criteria were enrolled. Clinical information, vital signs, spirometry results, and DLCO measurements were collected.

Results: There were 84 subjects participating in this study. The result of this study shows a 60.7% proportion of hypertension in stable COPD patients. Hypertension has a significant correlation with pulmonary functional values (*P=0.021*), severity degree of clinical COPD (*P=0.004*), Brinkman index (*P=0.008*), and age (*P=0.0001*). However, hypertension association with COPD duration (*P=0.505*) and DLCO (*P=0.122*) were not significant.

Conclusion: The hypertension proportion in stable COPD Indonesian patients is 60.7%. Hypertension shows a significant association with pulmonary function values, severity degree of clinical COPD, Brinkman index, and age.

Keywords: COPD, DLCO, hypertension, spirometry

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide.[1] Most of these deaths are related to cardiovascular disease.[2] This is due to systemic inflammation that causes increased vascular stiffness and hypertension. These comorbidities lead to poor quality of life, low exercise tolerance, and an increased risk of hospitalization.[3]

Past medical history is a factor that should be considered in COPD patients. Prior diagnoses of pulmonary hyperinflation, hypoxemia, pulmonary hypertension, and exacerbations increase COPD risk. Hereditary factors, such as genetics also play a role. Other studies suggest proinflammatory substances such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), present in COPD patients, can cause damage to other organs when entering systemic circulation.[4,5]

Environmental factors also contribute to the occurrence of COPD. A study by Ratnawati et al on 881 COPD-diagnosed patients, characterized by airflow limitation and alveolar damage, shows that 30% of the subjects are smokers.[6] Mahishale et al and van Remoortel et al reported that smoking history and lack of daily physical activity may be the main risk factors for developing comorbidities in COPD patients.[7,8] Additionally, continuous inhalation of harmful gases such as factory smoke, combustion, and pollution also increases the risk of COPD.[1,9]

COPD is characterized by irreversible abnormal dilation of terminal bronchioles (chronic bronchitis) and a reduction of gas exchange diffusion area (emphysema), leading to decreased gas diffusion.[10] These abnormalities are identified through spirometry examination which is known as the gold standard for COPD diagnosis.[1,9] In Addition, Diffusing Capacity for Carbon Monoxide (DLCO)

using the single-breath technique is frequently examined to assess patients' diffusion capacity.[11]

Hypertension is one of the modifiable risk factors of COPD yet is known globally as a major contributor to morbidity and mortality.[12] However, there has been no prior research on the proportion of hypertension among COPD patients in Indonesia. This study aims to report the proportion of hypertension among stable COPD patients in the Indonesian population.

METHODS

This was a cross-sectional study conducted at the National Respiratory Center Persahabatan Hospital. The subjects were selected using total sampling between February and March 2023. COPD patients admitted to the Asthma and COPD Polyclinic were enrolled after receiving informed consent. COPD was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease 2022 (GOLD) 2022 criteria.

Patients with a prior diagnosis of lung failure, interstitial lung disease (ILD), bronchial asthma, or active pulmonary TB were excluded from the study. Blood pressure was measured, systolic blood pressure (SBP) and diastolic blood pressure (DBP) results were recorded. Blood pressure was evaluated based on the following categories: normal SBP <130 and DBP <85; normal-high SBP 130–139 and/or DBP 86–89; grade 1 hypertension SBP 140–159 and/or DBP 90–99; and grade 2 hypertension SBP ≥160 and DBP ≥100. Patients with normal blood pressure who were taking antihypertensive medications were included. Blood pressure categories refer to the International Society of Hypertension (ISH) 2020.

RESULTS

A total of 84 patients diagnosed with COPD were included in the study. The subjects were mostly male with 73 subjects (86.9%). There were 67 subjects in the ≥60 years age group (79.8%), which is larger than the <60 years old group. Based on the pulmonary function test, 34 subjects (40.5%) were categorized as GOLD 2 and 32 subjects (38.1%) as GOLD 3. In terms of severity, most of the subjects were classified as Group D with 40 subjects (47.6%). The majority of the patients had experienced exacerbations with 55 subjects (65.5%), and 57 subjects had been diagnosed with COPD for ≥2 years (67.9%).

Blood pressure was examined and categorized. It was found that 45 subjects (53.6%) had normal blood pressure, 13 subjects (15.5%) had normal-high blood pressure, 23 subjects (27.4%) had grade 1 hypertension, and 3 subjects (3.6%) had grade 2 hypertension. In total, 51 subjects (60.7%) were diagnosed with hypertension.

Table 1. Basic characteristics of COPD patients

Characteristic	N	%
Gender		
Male	73	86.9
Female	11	13.1
Age		
<60 years old	17	20.2
≥60 years old	67	79.8
Pulmonary functional values		
GOLD 1 ($FEV_1 \geq$ 80% predicted)	11	13.1
GOLD 2 (50%≤FEV_1<80% predicted)	34	40.5
GOLD 3 (30%≤FEV_1<50% predicted)	32	38.1
GOLD 4 (FEV_1<30% predicted)	7	8.3
Severity degree of clinical COPD		
Group A	19	22.6
Group B	17	20.2
Group C	8	9.5
Group D	40	47.6
History of exacerbations		
Exacerbations	55	65.5
No exacerbations	29	34.5
COPD duration		
<2 years	27	32.1
≥2 years	57	67.9
Blood Pressure		
Normal	45	53.6
Normal-high	13	15.5
Grade 1 Hypertension	23	27.4
Grade 2 Hypertension	3	3.6
Hypertension Comorbid		
Under hypertension treatment	38	45.2
Newly diagnosed hypertension	13	15.5
Total patients of hypertension	51	60.7
No hypertension	33	39.3

Among them, 38 subjects (45.2%) had been previously diagnosed and were on routine hypertensive medication. The remaining 13 subjects

(15.5%) were newly diagnosed with hypertension. The basic characteristics of the subjects are presented in Table 1.

Hypertension cases were found in every GOLD category, with the number of subjects as follows GOLD 1 (5 subjects), GOLD 2 (22 subjects), GOLD 3 (20 subjects), and GOLD 4 (4 subjects). A significant association between pulmonary function values and hypertension incidence was reported (*P<0.05*). Subjects in each severity group were predominantly diagnosed with hypertension. Most patients with hypertension were in COPD groups C and D (34.5%). Chi-square analysis shows a significant association between COPD severity and hypertension (*P<0.05*). There were 15 subjects (17.9%) with COPD <2 years who had hypertension, compared to a non-hypertension group with 12 subjects (14.3%). This is fewer than the COPD ≥2 years group, which had 36 subjects (42.9%). There was no significant relation between COPD duration and hypertension (*P*>0.05).

Subjects with moderate and severe Brinkman index were mostly diagnosed with hypertension, namely 36 subjects (42.9%). In contrast, there were 15 non-smokers with hypertension (17.9%). There was a significant association between the Brinkman index and hypertension in COPD patients (*P<0.05*). COPD's association with hypertension is shown in Table 2.

This study found that subjects <60 years old mostly did not have hypertension (15.5%). In contrast, among subjects ≥60 years old, more than half (56%) were diagnosed with hypertension. Chi-square analysis found a significant relation between age and hypertension (*P<0.05*). It was observed that hypertension groups had a higher median age of 67 years (range: 44–82 years), while subjects with normal blood pressure had a lower median age of 61 years (range: 50–87 years). There was a significant association between mean age and hypertension in COPD patients (*P<0.05*).

Table 2. COPD association with hypertension

Variables	Hypertension	Non-hypertension	*P*
Pulmonary function scores (GOLD degree)			
GOLD 1 and 2	27 (32.1%)	18 (21.4%)	0.021*[a]
GOLD 3 and 4	24 (28.6%)	15 (17.9%)	
Severity of clinical COPD			
Group A and B	22 (26.2%)	14 (16.7%)	0.004*[a]
Group C and D	29 (34.5%)	19 (22.6%)	
Duration of COPD			
<2 years	15 (17.9%)	12 (14.3%)	0.505[a]
≥2 years	36 (42.9%)	21 (25.0%)	
Smoking (Brinkman index)			
No smoking and mild Brinkman index	15 (17.9%)	10 (11.9%)	0.008*[a]
Moderate and severe Brinkman index	36 (42.9%)	23 (27.4%)	
Age [median (min-max)]	67 (44-82)	61 (50-87)	0.002*[a]
<60 years old	4 (4.8%)	13 (15.5%)	0.000*[a]
≥60 years old	47 (56.0%)	20 (23.8%)	
DLCO values			
Normal	13 (15.5%)	4 (4.8%)	
Borderline and mild	13 (15.5%)	9 (10.7%)	0.122[b]
Moderate	18 (21.4%)	9 (10.7%)	
Severe	7 (8.3%)	11 (13.1%)	
FEV_1/FVC (mean±SD)	0.539±0.113	0.548±0.128	0.680[a]
Pulmonary Function Score (GOLD)			
GOLD 1	5 (6.0%)	6 (7.1%)	
GOLD 2	22 (26.2%)	12 (14.3%)	---
GOLD 3	20 (23.8%)	12 (14.3%)	
GOLD 4	4 (4.8%)	3 (3.6%)	

Note: *significant if *P*<0.05; [a]significance test using Mann-Whitney Test; [b]significance test using Kruskall-Wallis

This study shows moderate DLCO groups were most diagnosed with hypertension (21.4%). Chi-square analysis showed a significant association between DLCO values and hypertension (*P<0.05*). In contrast, the proportion of patients with decreased DLCO values was 38 subjects (74.5%). The distribution of mean values was similar for both subjects diagnosed with hypertension and those without. An unpaired t-test revealed no significant correlation between FEV_1/FVC ratio and hypertension in COPD patients (*P>0.05*)

DISCUSSION

In the present study, we determined the proportion of hypertension among stable COPD patients visiting the Asthma and COPD Polyclinic at the National Respiratory Center Persahabatan Hospital. This study also examined the relationship between pulmonary function and the severity of hypertension in COPD patients. Other research variables were analyzed to assess their relationship with hypertension.

Most of the subjects were male, comprising 86.9% of the sample. This finding is consistent with Singh et al, who reported that 73.6% of the COPD population in India were male.[13] A meta-analysis by Adeloye et al[14] indicated males have a 2.1-fold higher risk of developing COPD compared to females, due to a higher prevalence of smoking. In 2018, the Health Research Institution in Indonesia (RISKESDAS) reported that the prevalence of men smokers in Indonesia reached 63.2%, compared to only 4.8% among women.[15]

This study shows a 79.8% proportion of COPD patients in ≥60 years age group. The result is higher than the 44% proportion reported by Chen et al.[16] Several theories explain the increased proportion of COPD in individuals ≥60 years such as immunosenescence, decreased lung function, and environmental exposure.[14,17,18] Hussain et al reported a 47.8% incidence of hypertension in individuals over 40 years old without COPD, suggesting COPD as factors that increase hypertension.[19]

This study also shows that most patients suffering from COPD have reached the GOLD 2 criteria. A similar result was reported by Kharbanda et al indicating nearly 40% of COPD patients were categorized as GOLD 2.[20] The study by Ariawan et al shows that 64.5% of COPD patients have reached GOLD 2 severity.[21] This is due to persistent symptoms in GOLD 2 patients, which necessitate routine polyclinic visits for treatment. As for COPD severity, Group D was the largest group among others. These results are similar to Yang al, which showed 44% of COPD patients were categorized as group D.[22]

Another study by Ariawan et al reported that most COPD patients who visited the hospital had reached group D.[21] The severity is influenced by exacerbation frequency, which can be caused by infections, increased air pollution and exposure to chemicals in the work environment.[22,23] Additionally, the National Respiratory Center Persahabatan Hospital is a national referral hospital for respiratory disease. Therefore, COPD patients seen there are often in severe clinical conditions.

This study shows that 65.5% of patients had a history of exacerbations in the past year. Of these, 57.1% of subjects were from groups C and D, which have a higher risk of exacerbation. This result is similar to the Cui et al study that reported 62.7% of patients had experienced exacerbations in the past year.[23] These can be stimulated by infection, exposure in the work environment, smoking status, and educational status. Yang et al also show that 0.2–0.5 patients per year required hospitalization during exacerbation.[22]

According to IHS 2020, hypertension is defined as an increase of SBP ≥140 mmHg and/or DBP ≥90 mmHg at 2–3 examinations with an interval of 1-4 weeks when conducted at a clinic or health care facility.[24,25] In this study, subjects were newly diagnosed with hypertension.[26] Based on the blood pressure examination in this study, 31% of COPD patients had blood pressure ≥140/90 mmHg and 53.6% of patients had normal blood pressure. These results are by research conducted by Singh et al, who

found the prevalence of hypertension in COPD patients to be 38.7%.[13]

In this study, the proportion of hypertension in COPD patients at the National Respiratory Center Persahabatan Hospital was 51 subjects (60.7%). Of these, 38 subjects were previously diagnosed with hypertension and were on therapy, while 13 subjects were newly diagnosed with hypertension. This is similar to research conducted by Greulich et al which reported a similar figure of 70% proportion.[5] dos Santos et al, in a systematic review, also show the most common comorbid disease in COPD patients was hypertension, with 17–64.7% prevalence.[27]

This study shows consistent results with Kim et al, which reported a higher proportion of hypertension in COPD patients with GOLD 3 and 4 pulmonary function values.[28] Similarly, Mannino et al30 found that the risk of hypertension increased in patients with GOLD 3 and 4 criteria, with a relative risk value of 1.6 (95% CI=1.3–1.9). This can be due to severe airflow limitations in COPD patients in GOLD 3 and 4, causing ventilation-perfusion mismatches. Consequently, hypoxemia, pulmonary vasoconstriction, vascular remodeling, right ventricular diastolic dysfunction, systemic inflammation, arterial vascular stiffness, hypertension and other cardiovascular diseases occur.[29,30]

Repeated hypoxemia also causes overactivation of the sympathetic nervous system, leading to increased blood pressure and a higher incidence of hypertension.[4,30] Most patients with hypertension were in COPD group D, in line with a study conducted by Raherison et al, which found that hypertension was more prevalent in patients with severe COPD.[31] This was associated with more severe COPD symptoms, a higher risk of exacerbations and lower lung function.

The results of this study indicate no significant relationship between COPD duration and hypertension (P>0.05). This study also showed a lower incidence of hypertension in patients diagnosed with COPD in less than 2 years. These results align with Rodriguez et al, which show a lower incidence of hypertension in patients newly diagnosed with COPD.[32] This may be due to systemic inflammation that takes years to cause arterial blood vessel stiffness. Additionally, the patient's history of hypertension may have influenced the results of this study.[32] The incidence of hypertension seems to be more influenced by frequent exacerbations than the duration of COPD. During exacerbation, there is an increase in systemic inflammation, which causes endothelial damage, and vascular stiffness that ends with hypertension or cardiovascular diseases.[4]

It was found that there was a significant relationship between the Brinkman index degree and hypertension in COPD patients (P<0.05). This is consistent with Ismail et al research (43.1%), and slightly higher than Hanif's (56.71%).[33,34] The results of this research reinforce previous studies that clearly show an association between smoking and the incidence of hypertension in various study populations. Exposure to smoking and toxic substances plays a role in systemic inflammation that is caused by oxidative stress in endothelial cells. The process leads to the formation of various oxidants, which trigger the activation of transcription factors in proinflammatory cytokine genes. Activation of proinflammatory cytokines triggers the inflammatory process in endothelial cells.[35] Cellular senescence also contributes to hypertension occurrence in COPD patients.[13,27]

Chronic inflammation over a long period causes damage to various endothelial cell functions. This leads to a decrease in various vasodilator mediators such as nitric oxide, which triggers the vasoconstriction process. Consequently, blood vessel diameter decreases, increasing blood vessel pressure and resulting in hypertension.[4] Yang et al show that smokers have a higher prevalence of respiratory symptoms, a greater annual rate of decline in FEV_1, and a higher COPD mortality rate compared to non-smokers.[22]

This study shows a correlation between patients age and hypertension (P<0.05). The results align with Mannino et al, which show a higher prevalence of hypertension as age increases.[29] Vascular stiffness found in hypertension patients can caused by decreased anti-aging molecules which are identical to cellular senescence. Hypertension risk

also increases due to physical inactivity, obesity, diabetes and kidney disease. Moreover, longer exacerbations and chronic inflammation will reduce CD34+ cells that are involved in vascular repair.[4,30,36]

The total proportion of patients with decreased DLCO values in this study was 72.6%. This is slightly higher than the research by Ismail et al, which found that the proportion of DLCO reduction in COPD patients was 56.9%.[33] This is because COPD patients have chronic inflammation that triggers parenchymal damage. If it continues, emphysema might occur, reducing the diffusion surface area. The decrease in DLCO value is related to the reduction of alveolar-capillary gas exchange area, membrane thickening, and hemodynamic conditions. The reduced diffusion surface area decreases the diffusion capacity.[37,38]

A systematic review study conducted by Sin et al showed that a decrease in FEV_1 is a marker for an increased risk of cardiovascular disease morbidity and mortality. A decrease in FEV_1 <75–80% predicts a 75% increased risk of cardiovascular disease mortality. Compared to FEV_1, which can be affected by restrictive disorders, a decrease in FEV_1/FVC value is a specific indicator of respiratory disease. In this study, the relationship between FEV_1/FVC and hypertension showed a similar mean distribution between the two groups. There was no significant association between FEV_1/FVC and hypertension in COPD patients (P>0.05).[39]

This result differs from Engstrom et al, who found the highest value of FEV_1/FVC ratio ≥77.3% compared to the lowest value of FEV_1/FVC ≤66.3% had a cardiovascular disease risk of around 73%.[40] Subjects with a FEV_1/FVC ratio ≤70% had a 2.1-fold risk of myocardial infarction.[41] The Baltimore Longitudinal Study of Aging found that FEV_1 impairment in COPD patients was a strong independent predictive factor for cardiovascular disease morbidity and mortality.[42]

LIMITATION

The limitation of this study is that the cross-sectional design is not the most ideal for finding cause-and-effect relationships between variables. This study used blood pressure measurements at the clinic, which is the main standard for making a diagnosis of hypertension. However, independent blood pressure measurements outside the clinic, such as Home Monitoring Blood Pressure (HBPM) and Ambulatory Blood Pressure Monitoring (ABPM), have begun to be widely used and have various advantages. These measurement techniques should also be evaluated in future studies. This study also did not evaluate other comorbidities that could affect hypertension.

CONCLUSION

The proportion of stable COPD patients at the National Respiratory Center, Persahabatan Hospital, was 60.7%. There is a significant association between pulmonary function scores, severity, Brinkman index, age, and DLCO value with hypertension. However, there was no significant association between the duration of COPD and hypertension.

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CONFLICT OF INTEREST

All authors declare no conflict of interest in this study.

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for The Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 Report). Global Initiative for Chronic Obstructive Lung Disease, Inc.; 2023.

2. Valipour A, Aisanov Z, Avdeev S, Koblizek V, Kocan I, Kopitovic I, et al. Recommendations for COPD management in Central and Eastern Europe. Expert Rev Respir Med. 2022;16(2):221–34.
3. Aisanov Z, Khaltaev N. Management of cardiovascular comorbidities in chronic obstructive pulmonary disease patients. J Thorac Dis. 2020;12(5):2791–802.
4. Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? European Respiratory Review. 2018;27(149):180057.
5. Greulich T, Weist BJD, Koczulla AR, Janciauskiene S, Klemmer A, Lux W, et al. Prevalence of comorbidities in COPD patients by disease severity in a German population. Respir Med. 2017;132:132–8.
6. Ratnawati R, Kolewora YM, Yunus F, Susanto AD, Samoedro E. Prevalence of COPD Outpatient Based on COPD Diagnostic Questionnaire and Spirometry in Persahabatan General Hospital in Jakarta. In: American Thoracic Society 2019 International Conference. American Thoracic Society; 2019. p. A1608–A1608.
7. Mahishale V, Angadi N, Metgudmath V, Eti A, Lolly M, Khan S. Prevalence and impact of diabetes, hypertension, and cardiovascular diseases in chronic obstructive pulmonary diseases: A hospital-based cross-section study. J Transl Int Med. 2015;3(4):155–60.
8. Van Remoortel H, Hornikx M, Langer D, Burtin C, Everaerts S, Verhamme P, et al. Risk Factors and Comorbidities in the Preclinical Stages of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2014;189(1):30–8.
9. PDPI. PPOK (penyakit paru obstruktif kronik) diagnosis dan penatalaksanaan. Jakarta: PDPI; 2016.
10. Casanova C, Gonzalez-Dávila E, Martínez-Gonzalez C, Cosio BG, Fuster A, Feu N, et al. Natural Course of the Diffusing Capacity of the Lungs for Carbon Monoxide in COPD. Chest. 2021;160(2):481–90.
11. Hyatt RE, Scanlon PD, Nakamura M. Interpretation of Pulmonary Function Tests: A Practical Guide (Fourth edition). China: Wolters Kluwer; 2014. 35–41 p.
12. Brouwers S, Sudano I, Kokubo Y, Sulaica EM. Arterial hypertension. The Lancet. 2021;398(10296):249–61.
13. Singh DR. Prevalence of Hypertension in Patients with Chronic Obstructive Pulmonary Disease Attending Respiratory Medicine OPD. Int J Med Sci Clin Invent. 2017;4(12):3346–8.
14. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respir Med. 2022;10(5):447–58.
15. Kementerian Kesehatan RI. Laporan Nasional Riskesdas 2018. Laporan Nasional Riskesdas 2018. Jakarta; 2018.
16. Chen J, Yin Y, Zhang Y, Lin X, Chen T, Yang Z, et al. Chronic Obstructive Pulmonary Disease Prevalence and Associated Risk Factors in Adults Aged 40 Years and Older in Southeast China: A Cross-Sectional Study During 2019–2020. Int J Chron Obstruct Pulmon Dis. 2022;17:2317–28.
17. Zhao Y, Fang L, Wang Z, Fan J, Cong S, Wu J. Prevalence and Associated Factors of COPD among Hypertensive Patients aged 40 Years or Older in China, 2014 -15. Research Square. 2022.
18. MacNee W. Is Chronic Obstructive Pulmonary Disease an Accelerated Aging Disease? Ann Am Thorac Soc. 2016;13(Supplement_5):S429–37.
19. Hussain MA, Mamun A Al, Reid C, Huxley RR. Prevalence, Awareness, Treatment and Control of Hypertension in Indonesian Adults Aged ≥40 Years: Findings from the Indonesia Family Life Survey (IFLS). PLoS One. 2016;11(8):e0160922.
20. Kharbanda S, Anand R. Health-related quality of life in patients with chronic obstructive pulmonary disease: A hospital-based study. Indian Journal of Medical Research. 2021;153(4):459–64.

21. Ariawan W, Yunus F, Damayanti T, Nurwidya F. Rate of forced expiratory volume in one second and forced expiratory volume in one second/forced vital capacity decline among Indonesian patients with chronic obstructive pulmonary disease after a year of treatment. Int J Appl Basic Med Res. 2019;9(2):95–9.
22. Yang T, Cai B, Cao B, Kang J, Wen F, Chen Y, et al. Severity distribution and treatment of chronic obstructive pulmonary disease in China: baseline results of an observational study. Respir Res. 2022;23(1):106.
23. Cui Y, Dai Z, Luo L, Chen P, Chen Y. Classification and treatment of chronic obstructive pulmonary disease outpatients in China according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017: comparison with GOLD 2014. J Thorac Dis. 2019;11(4):1303–15.
24. Perhimpunan Dokter Hipertensi Indonesia. Konsensus penatalaksanaan hipertensi 2021: update konsensus PERHI 2019. Jakarta: Perhimpunan Dokter Hipertensi Indonesia; 2021. 1–6 p.
25. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334–57.
26. Perhimpunan Dokter Spesialis Kardiovaskular Indonesia. Pedoman tatalaksana hipertensi pada penyakit kardiovaskular. Jakarta: Perhimpunan Dokter Spesialis Kardiovaskular Indonesia; 2015. 1–2 p.
27. dos Santos NC, Miravitlles M, Camelier AA, Almeida VDC de, Maciel RRBT, Camelier FWR. Prevalence and Impact of Comorbidities in Individuals with Chronic Obstructive Pulmonary Disease: A Systematic Review. Tuberc Respir Dis (Seoul). 2022;85(3):205–20.
28. Kim SH, Park JH, Lee JK, Heo EY, Kim DK, Chung HS. Chronic obstructive pulmonary disease is independently associated with hypertension in men. Medicine. 2017;96(19):e6826.
29. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. European Respiratory Journal. 2008;32(4):962–9.
30. Mills KT, Stefanescu A, He J. The Global Epidemiology of Hypertension. Nat Rev Nephrol. 2020;16(4):223–37.
31. Raherison C, Ouaalaya EH, Bernady A, Casteigt J, Nocent-Eijnani C, Falque L, et al. Comorbidities and COPD severity in a clinic-based cohort. BMC Pulm Med. 2018;18(1):117.
32. García Rodríguez LA, Wallander MA, Tolosa LB, Johansson S. Chronic Obstructive Pulmonary Disease in UK Primary Care: Incidence and Risk Factors. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2009;6(5):369–79.
33. Ismail E, Yunus F, Damayanti T. Correlation between Measurement of Lung Diffusion Capacity Using Single Breath Methods (DLCO-SB) and COPD Group in Persahabatan Hospital Jakarta. Jurnal Respirologi Indonesia. 2021;41(4):260–71.
34. Hanif MA, Wiyono WH, Ratnawati, Prihartono J, Antariksa B, Zaini J. Skor gabungan curb 65 dan rasio kapasitas inspirasi kapasitas paru total sebagai prediktor mortalitas dan eksaserbasi pada PPOK dalam satu tahun [Tesis]. [Jakarta]: Universitas Indonesia; 2013.
35. Boyer L, Bastuji-Garin S, Chouaid C, Housset B, Le Corvoisier P, Derumeaux G, et al. Are Systemic Manifestations Ascribable to COPD in Smokers? A Structural Equation Modeling Approach. Sci Rep. 2018;8(1):8569.
36. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370(9589):765–73.
37. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for The Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2022 Report). Global Initiative for Chronic Obstructive Lung Disease; 2022.
38. Morrison NJ, Abboud RT, Ramadan F, Miller RR, Gibson NN, Evans KG, et al. Comparison of

Single Breath Carbon Monoxide Diffusing Capacity and Pressure-Volume Curves in Detecting Emphysema. American Review of Respiratory Disease. 1989;139(5):1179–87.

39. Sin DD, Wu L, Man SFP. The Relationship Between Reduced Lung Function and Cardiovascular Mortality. Chest. 2005;127(6):1952–9.
40. Engström G, Wollmer P, Hedblad B, Juul-Möller S, Valind S, Janzon L. Occurrence and Prognostic Significance of Ventricular Arrhythmia Is Related to Pulmonary Function. Circulation. 2001;103(25):3086–91.
41. Sin DD, Man SFP. Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases? Circulation. 2003;107(11):1514–9.
42. Tockman MS, Pearson JD, Fleg JL, Metter EJ, Kao SY, Rampal KG, et al. Rapid decline in FEV1. A new risk factor for coronary heart disease mortality. Am J Respir Crit Care Med. 1995;151(2 Pt 1):390–8.