JMU
Jurnal Medika Udayana

ISSN: 2597-8012 JURNAL MEDIKA UDAYANA, VOL. 14 NO.11, NOPEMBER, 2025

Received: 2025-01-03Revision: 2025-10-16 Accepted: 2025-10-30

PHARMACOTHERAPY PROFILE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN ELDERLY PATIENTS AT RSUP PROF DR. I.G.N.G NGOERAH DURING THE PERIOD OF JANUARY 2023 – DECEMBER 2023

Putu Adisti Cecilia Sujana[1], I Gusti Ayu Artini[2], I Gusti Made Gde Surya Chandra Trapika[3], Ida Ayu Alit Widhiartini[4]

[1]Medical Student, Faculty of Medicine, Udayana University

[2, 3, 4]Department of Pharmacology, Faculty of Medicine, Udayana University

e-mail: adisi.cecilia@student.unud.ac.id

ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a global health issue that is often undiagnosed, particularly among the elderly. Furthermore, elderly patients with comorbidities may receive multiple and varied therapies to address their conditions, which can lead to complex polypharmacy. Therefore, research is needed to describe pharmacotherapy profile of COPD in elderly patients. **Objective**: To describe the pharmacotherapy profile of COPD in elderly patients at Prof. dr. I.G.N.G Ngoerah Hospital. **Methods**: This study employs a descriptive quantitative method with a cross-sectional approach, with samples taken retrospectively from the medical records of elderly COPD patients at Prof. dr. I.G.N.G Ngoerah Hospital in 2023, according to inclusion and exclusion criteria. Data was collected via Google Forms and analyzed using Microsoft Excel. **Results**: The most used COPD therapy regimen is the LABA-ICS combination, specifically the combination of salmeterol and fluticasone propionate (54.2%) followed by the combination of budesonide and formoterol fumarate (26.5%). Supportive therapy commonly administered to patients, include mucolytic agents such as N-acetylcysteine (61.4%) and ambroxol (22.8%). The most common comorbidity diagnosed among COPD elderly patient was cardiovascular disease (54.3%), with most patients receiving beta-blocker medications that have the potential to cause drug interactions with β2-agonists. **Conclusion**: The use of dual LABA-ICS combinations with additional symptomatic therapy in the form of mucolytics such as N-acetylcysteine and ambroxol is the most common choice for controller therapy for outpatient elderly COPD patients at Prof. dr. I.G.N.G Ngoerah Hospital.

Keywords : Chronic Obstructive Pulmonary Disease (COPD), Elderly, Polypharmacy.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung condition that presents a major global health issue, with rising rates of incidence and mortality each year. In 2019, World Health Organization (WHO) reported 174 million cases and 3,23 million deaths, which was third leading cause of death worldwide. COPD is also recognized as a major contributor to poor health conditions globally, affecting approximately 16 million people in the United States alone, with millions more likely undiagnosed.[1] The prevalence of COPD dramatically increases with age, yet awareness and attention to the disease remain insufficient. Morbidity and mortality associated with COPD rise significantly in the elderly due to physiological changes in lung composition, anatomy, and function. Aging leads to decreased lung function and impaired tissue regeneration, exemplified by reduced alveolar flexibility, which diminishes gas exchange efficiency and increases susceptibility to infections.[2]

COPD rarely occurs without comorbidities among elderly patients. Comorbidities significantly impact prognosis and overall health status. Multimorbidity exacerbates disease burden, decreases quality of life, and complicates management strategies. Studies have identified 14 common comorbidities associated with COPD, including hypertension, coronary artery disease, diabetes, osteoporosis, depression, and chronic kidney disease. Cognitive impairments, particularly in verbal memory and constructive abilities, alongside depression, can overshadow clinical conditions and lead to premature mortality.[3,4] Elderly patients often require complex polypharmacy due to their multiple comorbidities, which increases the risk of adverse drug reactions. The significant physiological changes associated with aging such as altered metabolism and decreased drug clearance, increasing the risk of harmful drug responses. Therefore, pharmacotherapy decisions among elderly must be considered especially relating to pharmacokinetic and pharmacodynamic changes to optimize treatment while minimizing side effects.[5]

Common pharmacological treatments for COPD include inhaled bronchodilators from various classes such as β2 agonists, anticholinergics, methylxanthines, corticosteroids, and antibiotics. However, to date there is no precise guideline used for elderly patients with COPD; adult guideline therapy usually applied for

the treatment of COPD elderly patients. This lack of specificity complicates treatment regimens by necessitating considerations for comorbid conditions and age-related physiological changes. Research indicates that a significant portion of elderly patients—73.33% in one study are on multiple medications (3-4 drugs), with β2 agonists being used by 88%, corticosteroids by 70%, methylxanthines by 66%, and anticholinergics by 47%. Combination treatments have demonstrated efficacy in alleviating symptoms and enhancing overall well-being. [6,7]; however, existing studies do not specifically target elderly populations. Given the limited research on COPD pharmacotherapy in elderly patients in Bali, there is a critical need for comprehensive data collection regarding the pharmacotherapy profiles of elderly outpatients at Prof. dr. I.G.N.G Ngoerah Hospital in Denpasar.

MATERIALS AND METHOD

This study was a descriptive study using a retrospective case control method. Samples of this study were obtained by a total sampling of the medical records of elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital in Denpasar from January 2023 to December 2023. The study was conducted from September 2024 to December 2024 and was approved by the Research Ethics Commission of the Faculty of Medicine, Udayana University with protocol number 4399/UN14.2.2.V.1/PT.01.01/2024.

This study includes all elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital in 2023 recorded in the medical record and excludes those who has lung cancer and HIV as the comorbidities. The collected data was processed using Microsoft Excel and presented with table and graphic.

RESULT

Based on inclusion and exclusion criteria, there are 83 samples that were used in this study. According to **Table 1**, the number of patients was dominated by males, with a total of 50 patients (60.2%) compared to females, with a total number of 33 patients (39.8%). The highest prevalence of COPD cases in the elderly was found in the age group of 60-74 years, with a total of 47 patients (56.7%).

The data presented indicated that patients often complain of productive cough (62.6%) and shortness of breath (50.6%). These conditions were the most encountered clinical symptoms in COPD patients. The cough typically experienced was a productive cough with thick white sputum, without the presence of blood. Meanwhile, shortness of breath was usually felt to worsen when patients walk a considerable distance or engage in strenuous activities. Additionally, patients often complain of dry cough, chest pain, weakness, and chronic cough.

Table 1. Characteristics of elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital

Characteristics	n	%
Gender		
Male	50	60.2
Female	33	39.8
Age		
60-74 years old	47	56.7
75-90 years old	35	42.1
>90 years old	1	1.2
Clinical Symptoms		
Chronic cough	1	1.2
Productive cough	52	62.6
Shortness of breath	42	50.6
Weakness	3	3.6
Dry cough	8	9.6
Chest pain	5	6

In this study, only 23 patients (27.7%) were found to have undergone outpatient treatment with spirometry test results during the study period. The most common classification was patients undergoing outpatient treatment with moderate severity of COPD, which included 11 patients (47.8%). The results of this spirometry test are related to the classification of COPD based on the GOLD 2023 guidelines.

Table 2. Severity level of elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital

Severity Classification According to GOLD	n	%
Mild (FEV1 > 80%)	1	4.3
Moderate (FEV1 50-80%)	11	47.8
Severe (FEV1 30-50%)	5	21.7
Very severe (FEV1 < 30%)	6	26

Based on the GOLD 2023 guidelines. in addition to spirometry testing, COPD patients also undergo assessment using the COPD Assessment Test (CAT) and the Modified Medical Research Council (mMRC) scale. These assessments aim to evaluate the

severity of symptoms and guide treatment decisions for patients. In this study, elderly patients with COPD were predominantly classified in Group E (50.5%), exhibiting varied symptoms (mMRC grade > 2,
CAT score > 10. with a high risk of exacerbations).

Table 3. COPD Groups in Elderly Patients at Prof. dr. I.G.N.G Ngoerah Hospital

COPD Group According to GOLD	n	%
Stable COPD Group A	2	2.4
Stable COPD Group B	30	36.1
Stable COPD Group E	35	42.1
Acute Exacerbation COPD Group A	1	1.2
Acute Exacerbation COPD Group B	8	9.6
Acute Exacerbation COPD Group E	7	8.4

Based on **Tables 4** and **5**, there were 57 patients (68.7%) with comorbidities. indicating that the most of the elderly patients with COPD have comorbid conditions. The most prevalent comorbidity was cardiovascular disease. affecting 31 patients (54.3%), with congestive heart failure in 17 patients (29.8%), and hypertension in 14 patients (24.5%). This is followed by dyspepsia in 13 patients (22.8%) and pneumonia in 10 patients (17.5%).

Table 4. Comorbidities of elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital

Comorbidity	n	%
No comorbidity	26	31.3
With comorbidity	57	68.7

Table 5. Types of comorbidities in elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital

Comorbidity	n	%
Congestive heart failure	17	29.8
Hypertension	14	24.5
Dyspepsia syndrome	13	22.8
Pneumonia	10	17.5
Kidney disorders	6	10.5
Type 2 diabetes mellitus	5	8.8
Anemia	3	5.2
Benign prostatic hyperplasia	2	3.5
Atherosclerotic heart disease	2	3.5
Osteoporosis	1	1.7
Lower back pain	1	1.7
Glaucoma	1	1.7
Dementia	1	1.7

Based on **Figure 1**, the combination of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) was the most commonly used therapy for outpatients at Prof. dr. I.G.N.G Ngoerah Hospital. Mucolytic therapies using N-acetylcysteine and ambroxol were also widely utilized to address additional symptoms such as cough.

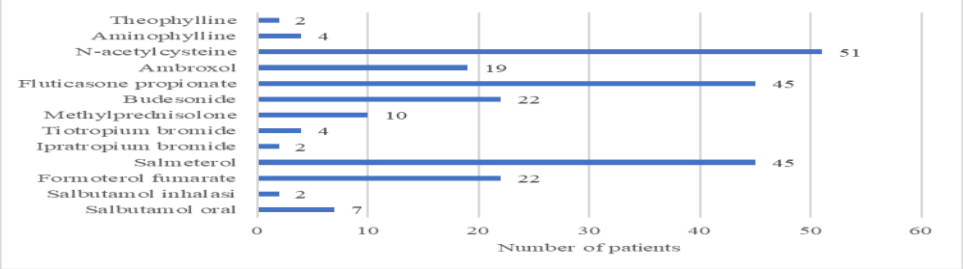

Figure 1. Therapy profile of elderly Patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital

Table 6. Pharmacotherapy dose regimen of elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital

Drug Class	Drug Name	Route	Frequency	n	%
β-2 Agonis	Salbutamol	Oral	2x1 (1 mg)	1	1.2
			3x1 (2 mg)	6	7.2
	Salbutamol	Inhalation	2x1 puff (100 mcg)	2	2.4
Xanthine	Aminophylline	Oral	1x1 (200 mg)	1	1.2
			2x1 (200 mg)	2	2.4
			3x1 (200 mg)	1	1.2
	Teophylline	Oral	1x1 (300 mg)	2	2.4
Corticosteriod	Methylprednisolone	Oral	3x1 (4 mg)	1	1.2
			3x1 (8 mg)	1	1.2
			2x1 (8 mg)	6	7.2
			2x1 (16 mg)	2	2.4
Antimuscarinic	Ipratropium bromide (Inhavent)	Inhalation	1x1 respul (500 mcg)	1	1.2
			1x3 respul (500 mcg)	1	1.2
	Tiotropium bromide (Sprivia)	Inhalation	1x1 puff (2.5 mcg)	1	1.2
			1x2 puff (2.5 mcg)	3	3.6
Mucolytic	Ambroxol	Oral	1x1 (30 mg)	4	4.8
			3x1 (30 mg)	15	18
	N-acetylsysteine	Oral	2x1 (200 mg)	1	1.2
			3x1 (200 mg)	48	57.8
			2x1 (600 mg)	2	2.4
Combination of inhaled corticosteroid and long acting bronchodilator	Budesonide and formoterol fumarate (symbicort)	inhalation	1x1 puff (160/4.5 mcg)	1	1.2
			2x1 puff (160/4.5 mcg)	21	25.3
	Salmeterol and fluticasone propionate (seretide diskus)	Inhalation	2x1 puff (100/50 mcg)	4	4.8
			2x1 puff (125/50 mcg)	1	1.2
			2x1 puff (250/50 mcg)	15	18
			2x1 puff (500/50 mcg)	25	30.1

The entire prescription of medication doses given to elderly patients shown in **Table 6** has been in accordance with the standard doses outlined in the British National Formulary 88.[8] The selection of medication types aligns with the GOLD guidelines, where patients in Group E are most frequently found to require combination and symptomatic COPD therapy. It was also explained that the majority of COPD medications were administered via inhalation routes, while oral medications were typically prescribed to relieve clinical symptoms in patients.

As can be seen on **Table 7**, there were 44 patients (53%) who consumed ≤ 3 medications. However, there were still patients who consumed more than 5 medications, categorized as polypharmacy, which included 17 patients (20.4%). It was related to the most common comorbidity found in elderly patients, which is cardiovascular disease, necessitating the need for multi-therapy.

Table 7. Number of Medications for elderly patients with COPD at Prof. dr. I.G.N.G Ngoerah Hospital

Number of Medications Consumed	Number of Patients	Percentage (%) N=83
≤ 3 medications	44	53
4 – 5 medications	22	26.5
6 – 9 medications	12	14.4
≥ 10 medications	5	6

DISCUSSION

This study aligns with the research by Reza et al. (2024), which states that men were more susceptible to COPD due to risk factors such as smoking habits, which were more commonly observed in males. The side effect of smoking did not show up immediately, these after-effect became much worse as they aged. Smokers were more likely to encounter respiratory symptoms and lung function irregularities, leading to a more significant annual decrease in Forced Expiratory Volume in one second (FEV1) than observed in females.[9,10] However, there was a narrowing gap between the incidence of COPD in men and women due to changes in smoking behavior and increased exposure to pollutants, leading to a rising incidence among women.[11]

The incidence of COPD will significantly increase with age, particularly in individuals over 60 years old. where its prevalence rises two to three times. This was consistent with the study by Gerungan et al. (2020), which found that the proportion of COPD patients was higher among those aged >60 years or in the elderly group. This correlates with the decline in lung function and capacity that occurs with aging, characterized by changes such as loss of elasticity and increased gas trapping in the lungs.[12]

Elderly patients's clinical symptoms with COPD were similar to those in other populations, such as productive cough with white sputum. shortness of breath during physical activity, chest pain. and dry cough. However, the manifestation of these symptoms can be more severe in the elderly due to the presence of comorbidities and a decline in physical capacity. [12] The symptoms experienced by patients significantly impact their daily activities; tasks such as climbing stairs, engaging in heavy activities, and walking long distances become increasingly limited. This indicates a decrease in quality of life and the ability to engage in normal daily activities for elderly patients.[13]

According to the GOLD 2023 guidelines, COPD patients were classified into four severity levels based on FEV1 values. Patients categorized as GOLD 1 (mild) had a better prognosis compared to those classified as GOLD 4 (very severe), who exhibit a higher risk of mortality and exacerbations.[10] Additionally, there was a classification of COPD patients through assessment into groups A, B, and E, where Group E represents the highest risk group, with a history of experiencing various levels of symptoms and exacerbations. Therefore, this group requires more attention in clinical management and prevention of complications. especially in elderly patients. Generally, patients in Group E are provided with combination therapy such as LABA/LAMA plus ICS or triple therapy.[10] This was also supported by the study of Moh et al. (2020), which indicated that a higher degree of obstruction based on FEV1 was associated with lower overall well-being and increased mortality.[14]

Elderly COPD patients were often followed with comorbidities, with cardiovascular and metabolic diseases being the most commonly found in this study. This was due to shared risk factors, such as daily lifestyle habits and increasing age. COPD was also frequently characterized by chronic inflammation, which can lead to systemic inflammation that contributes to the process of atherosclerosis, a common cause of heart diseases such as coronary artery disease and heart failure.[15] Several studies, including those by Eroglu et al. (2019) and Almagro et al. (2024), indicate that the most common comorbidities were metabolic diseases, cardiovascular diseases, and psychological disorders. Although the prevalence and ranking of comorbid diseases may vary across different studies, it was clear that cardiovascular and metabolic diseases remain the most prevalent among patients.[16,17]

The most commonly used therapy for elderly COPD outpatients at Prof. dr. I.G.N.G Ngoerah Hospital was the combination of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA). According to the study by Kristiningrum et al. (2020), in patients with moderate to very severe COPD and exacerbations, the combination of a long-acting beta-agonist (LABA) and inhaled corticosteroid (ICS) was more effective than using either treatment alone in enhancing lung function, improving health status, and decreasing the frequency of exacerbations.[18] The LABA and ICS combination provided a synergistic effect, where each drug enhances the therapeutic effect of the other. LABA offers long-term bronchodilation, while ICS addresses inflammation. allowing both to work optimally for maintenance therapy in COPD, However, the GOLD 2023 guidelines recommend using triple therapy (LABA-LAMA-ICS) over dual combinations. Triple therapy was considered more effective as it reduces the risk of exacerbations, improves lung function, and enhances the quality of life for patients. Nevertheless, researchers assume that dual combination medications were still more frequently prescribed due to considerations of cost. The expense of triple therapy tend to be higher for long-term treatment, as supported by the study by Rahmat et al. (2019).[19]

Patients with COPD often experience excessive sputum production and productive cough, making the use of mucolytics such as N-acetylcysteine and ambroxol highly recommended.[20] These mucolytic agents also possess antioxidant and anti-inflammatory properties, which can help reduce acute exacerbations in COPD patients. However, the use of ambroxol should be consulted, particularly in patients with a history of kidney or liver disease.[21]

In this study, the route of administration for maintenance therapy in COPD was primarily through inhalation, utilizing β-2 agonists, antimuscarinic agents, and combination therapies of inhaled corticosteroids and LABA. Additionally, patients were prescribed oral medications in tablet or capsule form to alleviate symptoms, such as xanthine derivatives and mucolytics. However, it is advisable to provide simple oral treatments with clear indications and minimal frequency to enhance adherence and reduce confusion.[8]

In this study, no dose adjustments or changes were observed during the repeated treatment of patients at Prof. dr. I.G.N.G Ngoerah Hospital. Dose adjustments in elderly patients were typically performed to evaluate and ensure that the prescribed medications do not cause side effects or toxicity.[7] It is recommended that pharmacokinetic testing be conducted on patients. However, in clinical practice. this was often not feasible due to the significant time, cost, and effort required to evaluate individual treatment profiles.

This study found better results compared to previous research which reported that 51% of home care patients used six or more medications daily, indicating a lower incidence of polypharmacy in this study. Nevertheless, there were still patients consuming more than five medications, categorized as polypharmacy, with 17 patients identified in this study. This was related to the fact that most elderly COPD patients also have cardiovascular diseases, necessitating multi-therapy. It was also known that patients with heart disease have a high risk of experiencing polypharmacy.[22]

According to the study by Fauziah et al. (2020), COPD patients with comorbid chronic heart failure experience drug interactions. The interacting medications include beta-blockers and beta2 agonists. Beta2 agonists such as salbutamol or formoterol can cause side effects that may exacerbate cardiac conditions, such as tachycardia and hypokalemia. Conversely, beta-blockers, especially non-selective ones like propranolol, can reduce the effectiveness of beta2 agonist therapy by inhibiting bronchodilation effects, potentially leading to bronchospasm or airway narrowing.[22] However, in this study, inhaled beta2 agonists were the most frequently chosen option because they act

locally and reduce systemic effects while increasing selectivity for beta-2 receptors, thereby minimizing side effects. It was also found that all patients with comorbid heart disease were prescribed cardioselective beta-blockers.

This study identified several patients with comorbidities such as diabetes mellitus, hypertension, and glaucoma receiving COPD therapy with corticosteroids either through inhalation or orally. The use of corticosteroids can elevate blood glucose levels and increase the potential for complications in diabetic patients. In hypertensive individuals, corticosteroid use can lead to sodium and water retention, contributing to elevated blood pressure. For patients with a history of glaucoma, corticosteroid use might increase intraocular pressure, potentially worsening their condition.

Polypharmacy due to comorbidities can be a risk factor for drug interactions. However, according to study of Fauziah et al. (2020), only a few have significant clinical implications, particularly in elderly patients. Therefore, careful monitoring of patient medication regimens is necessary to minimize the risk of side effects and ensure therapeutic effectiveness. [22]

CONCLUSION AND RECOMMENDATION

Elderly patients were found to have comorbidities, with cardiovascular and metabolic diseases being the most prevalent. The most commonly used COPD therapy regimen in elderly patients was a the combination of a long-acting beta-agonist (LABA) and inhaled corticosteroid (ICS). On average, each patient consumed approximately 3-4 different medications. Potential drug interactions may occur between COPD treatments involving beta2 agonists and congestive heart failure medications with beta-blockers, necessitating closer monitoring of elderly patients with both conditions.

Recommendations for future research include the need for in-depth analysis to further assess drug interactions experienced by elderly patients and the effects of these interactions. This study primarily presented the medication profiles and comorbidities of patients without sufficient depth, making it difficult to determine the prognosis of patients receiving such treatments.

REFERENCES

1. 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 May;10(5):447–58.
2. Matera MG, Hanania NA, Maniscalco M, Cazzola M. Pharmacotherapies in Older Adults with COPD: Challenges and Opportunities. Drugs Aging. 2023 Jul 14;40(7):605–19.
3. Mollica M, Aronne L, Paoli G, Flora M, Mazzeo G, Tartaglione S, et al. Elderly with COPD: comoborbitidies and systemic consequences. J Gerontol Geriatr. 2020 Oct;69(1):32–44.
4. Reynaert NL, Vanfleteren LEGW, Perkins TN. The AGE-RAGE Axis and the Pathophysiology of Multimorbidity in COPD. J Clin Med. 2023 May 9;12(10):3366.
5. Roblek T, Trobec K, Mrhar A, Lainscak M. Potential drug-drug interactions in hospitalized patients with chronic heart failure and chronic obstructive pulmonary disease. Arch Med Sci. 2014 Oct 1;10(5):920–32.
6. Teli A, Kumar A, Denod A, Ahmad A, Nain P. A Study of Drug Utilization and Prescribing Patterns of Drugs in Chronic Obstructive Pulmonary Diseased Patients (IPD and OPD) in Tertiary Care Hospital. Vol. 1, Acta Scientific Pharmacology. 2020.
7. Hathasary RH, Wiyono W, Mpila DA. Evaluasi Penggunaan Obat Pada Pasien PPOK (Penyakit Paru Obstruktif Kronis) Di Instalasi Rawat Jalan Rsup Prof. Dr. R.D. Kandou Manado. PHARMACON. 2021 Feb 24;10(1):630.
8. Joint Formulary Committee. British National Formulary 88.Airways disease, obstructive [Internet]. 2022. Available from: www.bnf.org/newsletter
9. Ngurah Bagus, M. P., Inten D. P., & Dinata, I. M. K. (2020). Hubungan antara rutinitas olahraga dengan fungsi paru pada perokok usia dewasa muda di Denpasar. Jurnal Medika Udayana, 9(7), 1-10. https://doi.org/10.24843/MU.2020.V9.i7.P08
10. GOLD. Global Initiative For Chronic Obstructive Lung Disease Global Strategy For The Diagnosis, Management, And Prevention Of Chronic Obstructive Pulmonary Disease (2023 Report) [Internet]. 2023. Available from: last accessed 20 October 2024
11. Zysman M, Raherison-Semjen C. Women's COPD. Front Med [Internet]. 2022 Jan 3;8. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.600107/full
12. Gerungan G, Runtu FB, Bawiling N. Karakteristik Penderita Penyakit Paru Obstruktif Kronis yang di Rawat Inap di Rumah Sakit Budi Setia Langowan. Epidemia. 2020 Nov;1(1):1–8.
13. Ciptaningrum I, Karyus A. Penatalaksanaan Holistik Pasien Tn. T Lansia 65 Tahun Dengan Penyakit Paru Obstruktif Kronis Melalui Pendekatan Kedokteran Keluarga. J Kesehat Tambusai [Internet]. 2022 Mar 7;3(1):46–57. Available from: http://journal.universitaspahlawan.ac.id/index.php/jkt/article/view/3740
14. Moh. Zamroni Lutfi, Arifianto, Mariyati. Hubungan Derajat Obstruksi Paru Dengan Kualitas Hidup Pasien Penyakit Paru Obstruksi Kronis (PPOK) di Rumah Sakit Paru dr. Ario Wirawan Salatiga. 2020;
15. Rothnie KJ, Connell O, Müllerová H, Smeeth L, Pearce N, Douglas I, et al. Myocardial Infarction

and Ischemic Stroke after Exacerbations of Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2018 Aug;15(8):935–46.
16. Eroglu SA, Gunen H, Yakar HI, Yildiz E, Kavas M, Duman D. Influence of comorbidities in long-term survival of chronic obstructive pulmonary disease patients. J Thorac Dis. 2019 Apr;11(4):1379–86.
17. Almagro P, Soler-Cataluña JJ, Huerta A, González-Segura D, Cosío BG. Impact of comorbidities in COPD clinical control criteria. The CLAVE study. BMC Pulm Med. 2024 Jan 2;24(1):6.
18. Kristiningrum E. Farmakoterapi Penyakit Paru Obstruksi Kronik (PPOK). Cermin Dunia Kedokt. 2019;46(4):262–71.
19. Rahmat J, Oktianti D. Evaluasi Pengobatan pada Pasien Penyakit Paru Obstruksi Kronis (PPOK) di RST Dr. Asmir Salatiga. Vol. 5, Journal of Holistics and Health Sciences. 2023.
20. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2019 May 20;2020(3).
21. Afina Dwi Rachmawati, Sulistiyaningsih. Penyakit Paru Obstruktif Kronis (PPOK). J. Farmaka. Vol. 18. 2023.
22. Fauziah H, Mulyana R, Martini RD. Polifarmasi pada Pasien Geriatri. Journal Human Care. Vol. 5. 2020.