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RESPIRATORY Science

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Original Article

The Association of Acquired Resistance EGFR Exon 20 T790M Mutation and Treatment Response in Lung Adenocarcinoma Patients Receiving EGFR-TKI

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Abstract

Background: Lung adenocarcinoma patients receiving EGFR-TKI may develop acquired resistance within 7-16 months of treatment initiation, which is characterized by the presence of exon 20 T790M mutations in treatment response patients and can be assessed objectively by CECT and then evaluated by RECIST 1.1. The purpose of this study is to look into the association between acquired resistance EGFR Exon 20 T790M mutation and treatment response in lung adenocarcinoma patients receiving EGFR-TKI.

Method: This research is an analytic study with a retrospective cohort design carried out at the Oncology Polyclinic at Haji Adam Malik Hospital from October 2020 to January 2021 in all patients with adenocarcinoma lung cancer who were treated with EGFR-TKI for more than 6 months. After that, an evaluation was carried out based on RECIST 1.1 and then examined for EGFR mutations from liquid biopsy specimens in the form of circulating tumor plasma DNA (ct-DNA) with the droplet digital Polymerase Chain Reaction (ddPCR) method to detect EGFR exon 20 T790M mutations as a marker of acquired resistance.

Results: It was found that the majority of subjects were female (64.5%), aged 20-69 years (58%), and non-smokers (67.7%). The most common EGFR mutation was exon 19 deletion (58.1%). The incidence of acquired resistance was found in 10 subjects (32.3%). The distribution of RECIST 1.1 results on positive acquired resistance includes progressive diseases of 35.2%; stable disease of 11.1%; partial response of 33.4%; and 100% complete response. Negative acquired resistance includes 64.8% progressive disease, 88.9% stable disease, 66.6% partial response, and 0% complete response (P=0.93).

Conclusion: There is no significant association between the incidence of acquired resistance mutations EGFR exon 20 T790M and treatment response in patients with lung adenocarcinoma who received EGFR-TKI therapy.

Keywords: Exon 20 T790M mutation, Acquired resistance, EGFR, Tyrosine Kinase Inhibitor, RECIST 1.1

INTRODUCTION

Lung cancer is the second most common cancer and the leading cause of cancer death in the United States. Around 247,270 new cases of lung cancer are estimated to occur in 2020, with 130,340 male cases and 116,930 female cases.[1] Indonesia ranks third after China and India, with the incidence of lung cancer, reaching approximately 25,322 cases with a mortality rate of 22,522 cases.[2]

Histopathologically, lung tumors are divided into two major parts, that is Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) which will later be divided into 2 subtypes, i.e. adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and unclassified lung carcinoma,[3] with the highest prevalence is the type of adenocarcinoma.[4–7]

Some people with lung cancer have mutations. Several studies have found a close relationship between mutations in the Epidermal Growth Factor Receptor (EGFR) gene, which is found in 15-20% of lung adenocarcinoma cases. In East Asia, the presentation of EGFR gene mutations in lung adenocarcinoma cases was higher, i.e. 35%, especially in stage III and IV. In India, EGFR gene mutations are expressed in 89% of lung adenocarcinoma cases.[8] Meanwhile, in Indonesia, research on adenocarcinoma lung cancer shows 44.4% EGFR mutations, namely common EGFR mutations (ins/dels exon 19, L858R), and uncommon EGFR mutations (G179X, T790M, L861Q) of around 57.1% and 29%.[9] In H. Adam Malik General Hospital, research on EGFR profile and RECIST 1.1 shows that at 3 months of Gefitinib treatment found Partial Response 38.5%, Stable Disease 46.2% and Progressive disease 15.4% while Erlotinib Partial Response 100%, Stable Disease 0%, Progressive disease 0%.[10]

EGFR mutations are usually found in the first four exons of the tyrosine kinase domain of the EGFR gene. The frequent mutations are as follows: Substitution for G719 in the nucleotide-binding loop of exon 18, in-frame deletion in exon 19, in-frame duplication and/or insertion in exon 20, and substitution for L858 or L861 in the activation loop of exon 21.[11] More than 80% of EGFR domain-mutated kinases have in-frame deletions at exon 19 or L858R exon 21.[12]

METHOD

This research is an analytic study with a retrospective cohort design that was held at the Oncology Polyclinic at Haji Adam Malik Hospital for 4 months from October 2020 to January 2021 in 31 patients with adenocarcinoma lung cancer and receiving Gefitinib, Erlotinib, or Afatinib who met the inclusion and exclusion criteria.

Medical records were reviewed for patient data, including the results of the EGFR gene mutation examination. Patients with EGFR no-mutation or EGFR mutation exon 20 T790M examination results at the beginning of the diagnosis were excluded from the study. The patient's medical record data was followed to see the

progress of the patient's disease during treatment. Patients with progressive disease from evaluation results or who have been on EGFR-TKI for at least 6 months were rebiopsied or liquid biopsied ct-DNA utilizing dd-PCR technique conducted at Prodia Laboratorium Medan to re-examine EGFR mutations. Data was obtained from the examination of EGFR exon 20 T790M mutations after treatment with EGFR-TKI (acquired resistance).

The univariate analysis was carried out to determine the profile and characteristics of lung adenocarcinoma patients with acquired resistance mutations EGFR exon 20 T790M and the description of the RECIST 1.1 results for the patients. The analysis was continued with a bivariate analysis that examined the relationship between the acquired resistance mutation EGFR exon 20 T790M and the patient's RECIST 1.1 results. Data analysis was done through the Chi-Square test or Fisher exact test.

In January 2009, a revised version of the RECIST 1.1 guide was introduced was introduced as a method of evaluating treatment response of oncology patients by assessing subjectively as a method of evaluating treatment response of oncology patients by assessing subjectively, semi-subjectively, and objectively using serial CECT to measure target lesions, non-target lesions, and new lesions.[13]

RESULT

There were 106 patients with a diagnosis of lung adenocarcinoma who had received targeted EGFR-TKI therapy. It was found that four patients who visited were still starting treatment in 2017. The four patients stated that their RECIST 1.1 results were for Progressive Disease.

A study was conducted to determine the relationship between the incidence of acquired resistance and RECIST 1.1 results in lung adenocarcinoma patients receiving tyrosine kinase inhibitor therapy. The demographic characteristics of the research subjects showed in Table 1.

Table 1. Demographic characteristics of research subjects

Characteristics	N	%
Gender		
Male	11	35.5
Woman	20	64.5
Age		
< 50 years	5	16.1
50 - 59 years	9	29.0
60 - 69 years	9	29.0
≥ 70 years	8	25.8
Ethnic group		
Batak	20	64.5
Jawa	8	25.8
Padang	3	9.7
Smoking Status		
Smoker	10	32.3
Never Smoker	21	67.7
Stage		
II B	1	3.2
III B	3	9.7
III C	1	3.2
IV A	20	64.5
IV B	6	19.4
Total	31	100.0

The molecular profiling and EGFR-TKI therapy response of the research subjects can be seen in Table 2.

All research subjects underwent gene analysis to detect mutations in EGFR by sequencing techniques. The results showed that of the 31 research subjects, the majority of subjects the majority of subjects (58.1%) had mutations in exon 19. Furthermore, mutations that were also

found in research subjects were mutations in exon 21, which were found in 10 subjects (32.3%). There were only 3 people (9.7%) of the subjects who had mutations in exon 18.

The majority of research subjects, namely 17 people (54.8%), got RECIST 1.1 progressive disease results. There were 9 patients whose RECIST 1.1 results were stable disease. There were 3 patients whose RECIST 1.1 results showed a partial response, and there were only 2 patients (6.5%) who managed to experience a complete response from the results of the RECIST 1.1 evaluation.

Table 2 demonstrates that, of the ten persons who had acquired resistance, six had progressing illness based on their RECIST 1.1 results. In other words, based on the results of the RECIST 1.1 review, the majority of patients who develop acquired resistance after receiving tyrosine kinase inhibitor treatment experience disease deterioration.

Table 2. Molecular profiling characteristics of research subjects

Characteristics	N	%
EGFR mutation		
Exon 18 G719X	2	6.5
Exon 19 Deletion	11	35.5
Exon 21 L858R	7	22.6
Exon 21 L861Q	2	6.5
Exon 18 G719D and Exon 21 L858R	1	3.2
Exon 19 Deletion and Exon 21 L861Q	1	3.2
Exon 21 L858R and Exon 21 L861Q	1	3.2
Exon 19 Ins/Del, Exon 21 L858R and Exon 21 L861Q	1	3.2
Types of EGFR-TKI		
Afatinib	2	6.5
Erlotinib	4	12.9
Gefitinib	24	77.4
Osimertinib	1	3.2
Length of Consumption TKI		
0-12 months	20	64.5
13-24 months	8	25.8
>24 months	3	9.7
RECIST 1.1 Results 1.1		
Progressive[8]	17	54.8
Stable	9	29.0
Partial	3	9.7
Complete	2	6.5
Acquired resistance		
Negative	21	67.7
Positive	10	32.3
Total	31	100.0

Table 3. Relationship of Exon 20 T790M Mutation (Acquired resistance) with RECIST 1.1

Exon 20 T790M Mutation (Acquired resistance)	RECIST 1.1 RESULT				P
	Pr (%)	S (%)	Pa (%)	Co (%)	
(+)	6 (35.2)	1 (11.1)	1 (33.4)	2 (100)	0.93
(-)	11 (64.8)	8 (88.9)	2 (66.6)	0 (0)	

Note: *Kurskal Wallis Test; Pr=Progressive; S=Stable; Pa=Partial; Co=Complete

This means that the occurrence of acquired resistance cannot be said to be the only factor that determines the occurrence of progressive disease in lung adenocarcinoma patients receiving tyrosine kinase inhibitor therapy. This is evidenced by the results of statistical analysis using Fisher's exact test, which showed that there was no relationship between the patient's RECIST 1.1 results and the incidence of acquired resistance EGFR exon 20 T790M (P>0.05).

DISCUSSION

Lung adenocarcinoma at a young age with the proportion of women who are not smokers obtained in this study can be a separate lung cancer entity. Several studies have reported the role of gene mutations in young lung cancer.[14] The PIONEER study reported the proportion of positive EGFR mutations for lung adenocarcinoma in 7 Asian countries ranged from 22-64%. This study found a high proportion of positive EGFR mutations in the young age group (70.8%), and this is higher than the old age (51.6%). This confirms the association of EGFR mutations as oncogene activators in young-onset lung adenocarcinoma. The proportion of wild type (29.2%) at a young age also needs further analysis because it does not mean that there are no gene mutations.[15]

The ddPCR method is the second difference, based on research showing that ddPCR and ARMS-PCR have high specificity with practical sensitivity for detecting EGFR mutations in cfDNA, which supports their application as a supplement or conditional alternative to tissue biopsy in clinical practice for genotyping. It seems that ddPCR has a higher sensitivity than ARMS-PCR, especially in the early stages.[16]

First-line therapy is given to patients who have never received previous treatment. If it turns out that the EGFR mutation is known early on, then EGFR-TKI therapy immediately becomes the first-line therapy option. On the other hand, if the EGFR mutation is negative, then platinum-based chemotherapy is the treatment option. Furthermore, after the administration of EGFR-TKI, progress was observed. If there is a worsening of the disease caused by the T790M mutation, the next treatment option can be given as second-line EGFR-TKI (Osimertinib).[17]

Adenocarcinoma patients with EGFR mutations will initially respond very well to EGFR-TKI therapy, but subsequently develop secondary resistance or resistance to the drug for an average of 9-14 months.[17,18] In the trial of the AURA3 study, using DNA testing without cells, it was found that about 51.2% of patients had the T790M mutation. This is why 60% of patients who have received EGFR-TKI eventually develop an EGFR T790M mutation at exon 20, which has been investigated as being associated with molecular changes.[19]

There are several mechanisms for the occurrence of resistance to EGFR-TKI, such as secondary mutation (T790M), activation of alternative pathways (c-Met, HGF, AXL), abnormalities at the end of the pathway (K-RAS mutation, loss of PTEN), and

disruption of the EGFR-mediated apoptotic pathway, TKI (polymorphisms in the form of deletion of the 11/BIM gene such as BCL2), histologic changes, ATP-binding transporter site (ABC) fusion, and others.[19,20] This mutation causes tridimensional alterations in the tyrosine kinase domain structure, preventing erlotinib and gefitinib from binding to the EGFR.[12]

Osimertinib is a potent and irreversible EGFR-TKI, selective for EGFR-TKI mutations and resistance T790M mutations, but has minimal effect on wild-type EGFR. The phase 2 study of the AURA trial demonstrated the efficacy and safety required for obtaining approval from the US Food and Drug Administration in the treatment of patients with EGFR T790M-NSCLC positive who had progressed during or after TKI therapy by demonstrating an objective response rate of 62%, and survival. Progression-free survival (PFS) ranges from 12.3 months.[21]

This study found that 10 people experienced acquired resistance. There were 6 people whose RECIST 1.1 results showed progressive disease. In other words, it can be interpreted that the majority of patients who experience acquired resistance after giving tyrosine kinase inhibitor therapy experience worsening of the disease based on the results of the RECIST 1.1 evaluation. However, at the same time, of the 21 people who did not experience acquired resistance, 11 of them also experienced progressive disease. This means that the occurrence of acquired resistance cannot be said to be the only factor that determines the occurrence of progressive disease in lung adenocarcinoma patients receiving tyrosine kinase inhibitor therapy.

However, the researcher admits that further studies are needed to detect the incidence of acquired resistance using specimens from rebiopsy tissue so that more accurate results can be obtained. In addition, the detection of acquired resistance events should be made a routine procedure for all adenocarcinoma patients after 9-12 months of receiving tyrosine kinase inhibitor therapy.[21]

This research received a special grant from Astrazeneca company and Prodia Laboratory, Medan.

CONCLUSION

The incidence of acquired resistance in lung adenocarcinoma patients receiving tyrosine kinase inhibitor therapy was 32.3%. There is no association between the incidence of acquired resistance and RECIST 1.1 results in lung adenocarcinoma patients receiving tyrosine kinase inhibitor therapy.

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Original Article

Vitamin C Supplementation Improves Pulmonary Tuberculosis Patients' Sputum Conversion During Intensive Phase Category I Treatment in Medan

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Abstract

Background: Many factors influence the success of the acceleration of Acid-Fast Bacilli (AFB) sputum conversion in the treatment of the intensive phase of pulmonary tuberculosis (TB). One of these factors is the nutritional status or nutrition of pulmonary TB patients. Through a fenton reaction, Vitamin C is known to be able to sterilize Mycobacterium tuberculosis. This study aims to determine the effect of giving vitamin C on the conversion of AFB sputum in the intensive phase of pulmonary TB treatment.

Method: This study was an inferential, quasi-experimental evaluation of the acceleration of AFB sputum conversion following vitamin C supplementation in patients with category I pulmonary TB. The study group was separated into two groups: 40 TB patients getting Anti Tuberculosis Treatment (ATT) with vitamin C, and 40 TB patients receiving ATT with placebo. Every two weeks, AFB sputum was examined, and vitamin C levels were measured before and after two months of therapy.

Results: Conversion of AFB occurred sooner in the vitamin C group of pulmonary TB patients, with as many as 29 patients (72.5%) experiencing conversion of AFB sputum at the end of the second week of therapy, whereas there was no conversion in the placebo group. At the end of the fourth week, all patients (100%) given vitamin C showed AFB sputum conversion, whereas only eight patients (20%) in the placebo group had conversion at the end of the fourth week of treatment. Vitamin C levels increased significantly in the group of pulmonary tuberculosis patients who received vitamin C supplementation.

Conclusion: Vitamin C supplementation in the treatment of pulmonary TB can accelerate the conversion of AFB sputum, which is statistically significant.

Keywords: *Mycobacterium tuberculosis*, vitamin C, AFB sputum conversion

INTRODUCTION

Pulmonary tuberculosis (pulmonary TB) is a direct infectious disease caused by TB germs, namely *Mycobacterium tuberculosis* (*M. tuberculosis*). In 2019, the incidence of tuberculosis in Indonesia was the 3rd highest in the world after India and Tiongkok, contributing 8.5% of TB cases worldwide, with 92000 deaths per year in Indonesia, and an additional 4700 deaths from HIV TB.[1]

Active TB patients are often associated with lower nutritional status compared to healthy people.[2] Micronutrient deficiencies and poor general nutritional status in active TB patients can suppress the cell-mediated immune system, which is the host's main defense against *M. tuberculosis.*[3] Giving vitamin C to TB patients can improve nutritional status by increasing appetite[4] and iron absorption, which are involved in fenton reactions.[5]

Vitamin C (ascorbic acid) is a water-soluble vitamin that belongs to a class of antioxidant vitamins that can inhibit the exchange of extracellular free radicals. Vitamin C functions as both an antioxidant and a pro-oxidant. The sterilization of vitamin C has an antioxidant impact on *M. tuberculosis* culture. The capacity of vitamin C to sterilize *M. tuberculosis* cells is due to an increase in ferrous ion concentration, which causes an increase in ROS generation, lipid alterations, redox imbalances, and DNA damage. Vitamin C penetrates the cells of *M. tuberculosis* and converts ferric ions to ferro ions. Through the Harber-Weiss and Fenton reaction, it produces superoxide, hydrogen peroxide, and hydroxyl radicals when combined with oxygen. This ROS production will damage DNA, disrupt lipids, and disturb redox equilibrium.[5]

This is the groundwork for studying the impact of vitamin C on the acceleration of the conversion value of AFB sputum in pulmonary TB patients with positive smear sputum in the intensive phase treament.

METHOD

The design of this study is quasi-experimental and was conducted in Medan in 2017 for six months. The study population included new cases of pulmonary tuberculosis in the intensive phase category I who were treated at H. Adam Malik Medan Hospital, Balai Pengobatan Penyakit Paru (BP4) Medan, and several health centers in Medan who met the study's inclusion and exclusion criteria and were willing to participate in the study by signing an informed consent letter.

The subjects in this study were pulmonary TB patients with positive smear examination who had never been treated with anti tuberculosis treatment (ATT) before, aged 20 to 65 years, HIV-negative patients, no gastric and liver disorders, non-diabetic, did not use immunosuppressive drugs, and were not pregnant or breastfeeding. Patients with pulmonary TB were selected at random using inclusion/exclusion criteria. According to the sample size calculation in this study, there were 80 active pulmonary TB patients participating, and after a simple

quota randomization was carried out in parallel studies, it was revealed that each 40 pulmonary TB patients were supplemented with vitamin C (500 mg Ester type 500 mg/day) with standard tuberculosis treatment, while the second group was given placebo with standard tuberculosis treatment.

AFB sputum examination was carried out microscopically, which was examined every 2 weeks for 2 months of treatment, and vitamin C levels before and after 2 months of treatment were examined using ELISA techniques. Data were descriptively analyzed to determine the frequency distribution of research subjects based on their characteristics, and then inferentially analyzed to determine the difference in AFB sputum conversion after the administration of vitamin C plus ATT versus placebo plus ATT. To find out the relationship between vitamin C levels and AFB conversion, the chi-square test can be used if it fulfills the requirements, and if not, an alternative test, namely the Wilcoxon Signed Ranked test, The collected data was processed and analyzed with 95% confidence intervals and significance levels of P<0.05.

RESULT

The demographic characteristics of TB patients who received Vitamin C with ATT and placebo with ATT were described in Table 1. Sex and age differences were not significant between the Vitamin C and placebo groups.

Table 2 shows that AFB conversion in all patients (100%) who were given vitamin C supplementation occurred at the end of the fourth week of treatment, but only eight subject (20%) in the placebo group with ATT. Conversion of AFB sputum continued until the end of the study, which was assessed every 2 weeks during the intensive phase of treatment. This study proves that there are significant differences (P<0.05) after 8 weeks of vitamin C supplementation.

Table 1. Demographic characteristics of subjects

Characteristic	Treatment	
	Vitamin C with ATT (n = 40)	**Plasebo with ATT (n=40)**
Gender		
Male	28 (70%)	25 (62.5%)
Female	12 (30%)	15 (37.5%%)
Age		
20-40 years	19 (47.5%)	20 (50.0%)
40-60 years	18 (45.0%)	17 (42.5%)
>60 years	3 (7.5%)	3 (7.5%)
Positivity of AFB		
1+	24 (60.0%)	29 (72.5%)
2+	14 (35.0%)	10 (25.0%)
3+	2 (5.0%)	1 (2.5%)

AFB conversion was found to be 100% (40/40) in the Vitamin C with ATT group and 20% (8/40) in the placebo group with ATT, described in Table 3, where the addition of Vitamin C in TB management was more effective than giving ATT alone (P<0.05).

Table 2. Treatment and AFB sputum conversion

Characteristic	Treatment	
	Vitamin C with ATT (n = 40)	**Plasebo with ATT (n=40)**
Conversion AFB		
1st Month	40 (100%)	8 (20%)
2nd Month	0 (0%)	32 (80%%)
Conversion AFB Based on		
2 weeks	29 (72.5%)	0 (0%)
4 weeks	11 (27.5%)	8 (20%)
6 weeks	0 (0%)	25 (62.5%)
8 weeks	0 (0%)	7 (17.5%)

Table 3. Treatment and the Conversion of AFB sputum in One and Two Months

Treatment	AFB Conversion		Total	P
	1st month	2nd month		
Vitamin C with ATT	40 (100%)	0 (0%)	40 (100%)	0,0001
Plasebo with ATT	8 (20%)	32 (80%)	40 (100%)	
Total	48 (60%)	32 (80%)	80 (100%)	

Note: Paired T-test

Table 4. Vitamin C Level Before and After 2 Months Treatment

Mean level of vitamin C (ng/dL)	Treatment	
	Vitamin C with ATT (n=40)	Placebo with ATT (n=40)
Before	73.39±25.53	74.59±25.51
After	372.84±36.06	161.66±35.79
Difference	299.45±31.56	87.05±39.60
P	0.0001	0.0001

Note: Paired T-test

The results of the paired t-test analysis showed a significant difference in vitamin C levels after 2 months of treatment in both groups (P<0.05). But the increased in vitamin C level is higher in subjects with vitamin C supplementation than in subjects with placebo. In the vitamin C supplementation group, the difference in vitamin C level before and 2 months after ATT was 299.45±31.36 ng/dl compared to 87.05±36.90 ng/dl in the placebo group (Table 4).

DISCUSSION

The characteristics of this study are based on age, namely 20–40 years old for 39 people. As many as 35 people, and aged >60 years, as many as 6 people. The most is in the age group 20–40 years, with as many as 39 people (48.75%). The sex in this study was more in men than in women, with 70% in the group given vitamin C and 62.5% in the group not given vitamin C.

Conversion of sputum AFB in the vitamin C with ATT supplementation group occurred in the second week was 72.5% and 0% in the placebo group with ATT. Conversion of AFB sputum continued until the end of the study which was assessed every 2 weeks during intensive phase treatment. This study proves that there are significant differences after 8 weeks of vitamin C supplementation (P<0.05).

A study by L. Susanto et al. found significant results for AFB sputum culture. In pulmonary TB patients who received vitamin C supplementation in the second week, 6.1% had negative sputum cultures, whereas none in the control group hadIn six and eight weeks, 93.5% and 100% of TB patients with vitamin C supplementation had negative sputum cultures, compared to 54.8% and 83.9% in the control group.[6] In this study, the administration of vitamin C significantly increased vitamin C levels in both groups with vitamin C and placebo. The increase in vitamin C levels, on the other hand, was greater in the group that received vitamin C supplementation.

A study in New Zealand in healthy populations found that plasma vitamin C levels increased to >70 µmol/L from <50 µmol/L (P<0.001) in one week of vitamin C supplementation and continued to increase in vitamin C status after a four-week intervention (P=0.016). There was a 20% increase in the chemotaxic function (P=0.041) and the oxidant generation

function of neutrophil cells (P=0.031) after the intervention of vitamin C supplementation.[7]

In the body, vitamin C functions in several metabolic processes, including: 1) as a cofactor for a number of hydroxylation reactions, 2) catalyst nitric oxide (NO) degradation of heparin sulfate, and 3) redox homeostasis in the mitochondrial respiration process. In vivo studies show that ascorbate concentrations in mammalian mitochondria can be increased by dietary supplements of vitamin C.[8]

Several studies stated that antioxidants found low in TB patients are glutathione, ascorbic acid (vitamin C), and α-tocopherol (vitamin E). Low antioxidant levels are caused by insufficient intake in pulmonary TB patients and increased free radicals during the process of phagocytosis of *M. tuberculosis*.[9,10]

In pulmonary TB patients who receive treatment, one indicator of evaluating the progress of therapy is the determination of sputum conversion. Many factors influence the success of AFB sputum conversion in intensive TB treatment.[11]

One study found that one of the factors that influenced the success of AFB sputum conversion in intensive phase treatment was the patient's initial nutritional status when diagnosed with TB.[2] This is because TB infection increases leptin production, which causes loss of appetite and decreased nutrient intake, resulting in a deficiency of calories and protein.[11]

The most frequent side effects from the administration of vitamin C are heartburn, nausea, and vomiting. In this study, it is very rare for us to find a complaint in the patients we gave supplemental vitamin C supplementation in the treatment of intensive pulmonary TB, perhaps because the vitamin C capsules given were slow in absorption in the body, thereby reducing side effects in patients.

In terms of the price per capsule, which is around two thousand rupiah per tablet of vitamin C, the supplementation of vitamin C to TB treatment can be considered because cost-effectively accelerating the conversion of AFB sputum smear can break the chain of transmission in the community.

The findings of this study may be used by health professionals to offer additional vitamin C supplements to pulmonary TB patients in treatment, as well as by the health department to develop a policy including vitamin C into the treatment of pulmonary TB in the intensive phase.

The limitation of this study is that the number of subjects with an AFB 3+ sputum smear was less than those with an AFB 2+ or 1+. Further research is needed with a larger number of AFB 3+ sputum smear subjects and better recording of side effects.

CONCLUSION

In pulmonary tuberculosis patients receiving category I anti-tuberculosis treatment during the intensive phase, vitamin C supplementation can accelerate the conversion of AFB sputum.

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Original Article

Neutrophyl – Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP) Levels in Stable and Exacerbated Chronic Obstructive Pulmonary Disease (COPD) Patients in Persahabatan Hospital Jakarta

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Abstract

Background: Although COPD has been believed to be characterized by respiratory disease, there are currently limited study conducted to evaluate inflammation markers and exacerbation rate in COPD by noninvasive methods. We did a prospective cohort study to observe the alteration of Neutrophyl-Lymphocyte Ratio (NLR) and C-reactive protein (CRP) in COPD patients to find any possible correlation with COPD exacerbation status.

Method: From July to December 2018, a prospective cohort study was performed with blood and spirometry test on 31 COPD patients during exacerbation (AE-COPD) and stable. The mean of NLR and CRP were compared and analyzed.

Results: Both NLR and CRP decreased during stable condition (from 7.95±6.8 to 4.6±5.5 and 43.4±71 to 12.2±18.5) with P<0.01 respectively. We also found a significant inverse correlation between NLR and FEV_1/FVC in AE-COPD and CRP showed an inverse correlation only with FEV_1 in AE-COPD. Another interesting finding was a subject with very high CRP whose value remained above the nomal limit during stable, and died within 2 months after exacerbation.

Conclusion: NLR and CRP levels in COPD patients increased during exacerbation, which may reflect lung function and exacerbation status.

Keywords: neutrophil, lymphocyte, COPD, NLR, CRP

INTRODUCTION

Several previous studies have concluded that neutrophils are the dominant cells exacerbating COPD.[1–4] In addition to airway conditions, COPD has the characteristics of a systemic inflammatory disease.[5] Research in recent years has proven the value of the neutrophil-lymphocyte ratio (NLR) in blood samples as a potential marker of systemic inflammation.[6] In 2014, Günay et al. concluded NLR could be used as an inflammatory marker to assess the degree

of inflammation in COPD. This NLR test is characterized as fast, inexpensive, and easy.[7]

Research on NLR showed an association between NLR and airflow limitation, disease severity, exacerbations, hospitalizations, and mortality in COPD.[8–11] Considering COPD has systemic inflammation characteristics, this study will also assess C-reactive protein (CRP), which was stated to be increased in patients with acute exacerbated COPD (AE-COPD) compared to stable conditions.[5,9] Research that found evidence that the NLR in AE-COPD was higher than stable COPD was mostly designed as cross-sectional or retrospective.[9–11] In Indonesia, there is no COPD research focused on NLR or CRP yet.

METHOD

This study is a descriptive-analytic with prospective cohort design. It was carried out at the emergency department and outpatient clinic of Persahabatan Hospital Jakarta from July 2018 to December 2018. A total of 31 AE-COPD patients who met the inclusion criteria were subjected to spirometry and blood tests and then followed up for one month after the exacerbation to be re-examined when their condition was stable.

No patients complained of shortness of breath since childhood or experienced shortness of breath before smoking. Patients with possible Post-Tuberculosis Obstructive Syndrome (SOPT) were excluded through history taking and chest X-rays during the inclusion process.

All data obtained were analyzed using SPSS 20.0 *for windows*. Saphiro Wilk normality test was done to determine the data distribution with fewer than 50 subjects followed by a comparison test of two mean paired data sets with Wilcoxon and paired t-test, respectively to the normality test results. Spearman or Pearson was used to find a correlation.

RESULT

This study recruited 39 AE-COPD patients who met inclusion criteria. Eight patients did not participate until the analysis step due to drop outs: 2 patients dealt with administration regarding the referral process, 4 patients lost contact and did not show up on the specified date, and 2 patients withdrew themselves. Therefore, 31 patients participated in this study until the final stage.

The average age was 62±1.5 years, with Body Mass Index (BMI) of 21.8. Airway obstruction severity according to the GOLD criteria (defined by percentage of FEV_1/predicted FEV_1) shows that most of the patients in this study were GOLD II criteria (25 patients - 80.6%). In GOLD III group, there were 5 patients (16.3%), and only one patient included in GOLD I criteria. There were no patients who met GOLD IV.

In both exacerbation and stable conditions, the patient filled out a form, resulting in two CAT scores being obtained for each patient. The average CAT score in AE-COPD was 15.4±3.8, while stable was 12.2±2.4. Only two patients (6.45%)

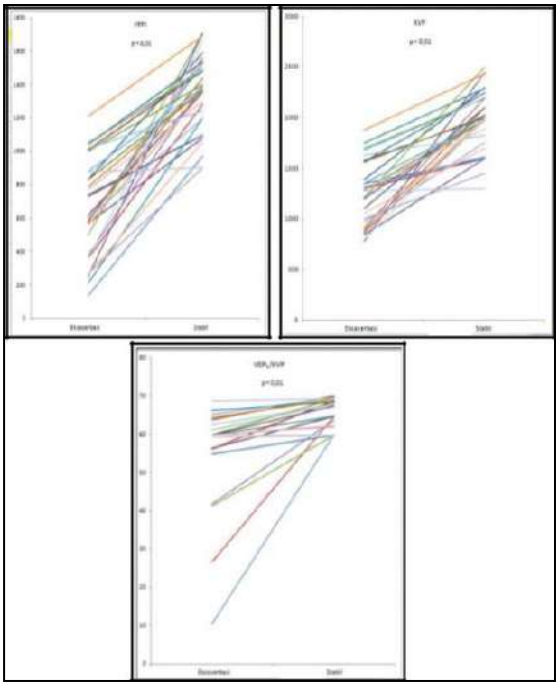
showed similar CAT scores while 93.5% experienced a decrease in CAT scores during stable (P<0.01). There were no patients with higher CAT scores during AE-COPD.

Table 1. Characteristics of the research patients

Characteristics	Subject N = 31
Age (years)	62±1.5
Body Mass Index (BMI)	21.8
Smoking status	
Active	2
Ex-smoker	29
Brinkmann Indeks Index	
Mild	0
Medium	5
Heavy	26
Pre-bronchodilator spirometry (*obtained during stable)*	
FEV_1	1387.2±40
FVC	2046.4±52
FEV_1/FVC	62.4±0.7
Post-bronchodilator spirometry (*obtained during stable)*	
FEV_1	1532.4±41.5
FVC	2354±70
FEV_1/FVC	65.2±0.6
GOLD* Criteria	
I	1
II	25
III	5
IV	0

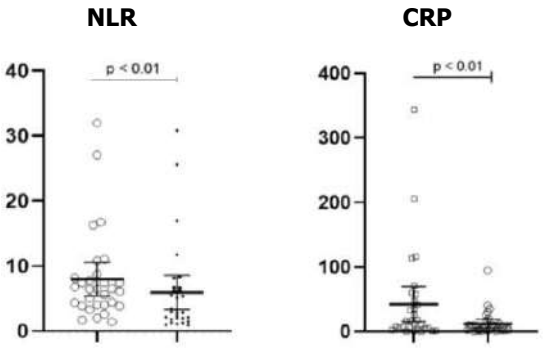
Note: *GOLD: Global Initiative for Obstructive Lung Disease

The results obtained showed that the FEV_1 and FVC values were lower in AE-COPD. The average FEV_1 was 666.29±52 (AE-COPD) and 1350±41 (stable). Data with n<50 using the Saphiro-Wilk showed P>0.05 (normal distribution), resulting in paired t-test analysis was used for comparison of two paired means. Based on the study, the results were statistically significant with P<0.01. Meanwhile, the FVC also showed a statistically significant difference, 1258.38±55 in AE-COPD and 1978±53 at stable (P<0.01).



Graphic 1. Changes in the patient's pulmonary function in exacerbation and stable conditions

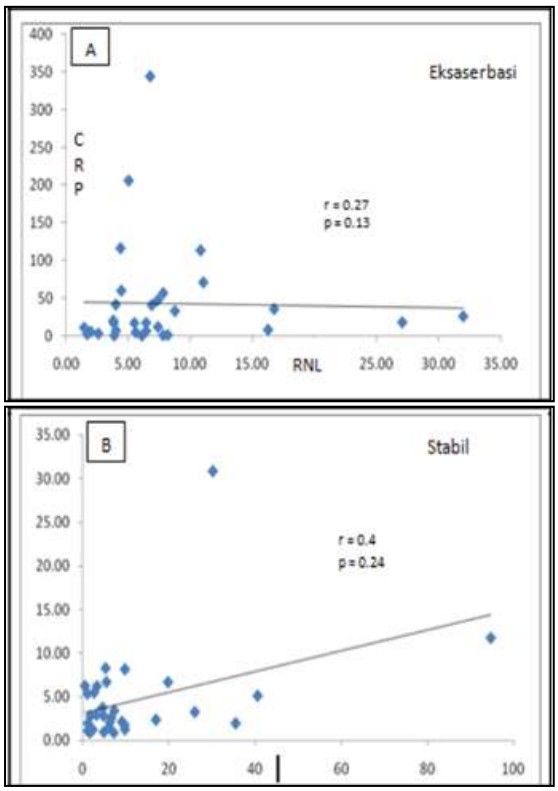
Airway obstruction characterized by FEV_1/FVC also changed. In AE-COPD, FEV_1/FVC was lower (56.8±2 vs 64±0.8). The FEV_1/FVC data distribution was not normal, Wilcoxon test was used to compare the two paired mean data. The analysis showed P<0.01. Changes in FVC and FEV_1 values in these two different conditions are shown in Graphic 1.



Graphic 2. Average NLR and CRP values in exacerbation and stable conditions

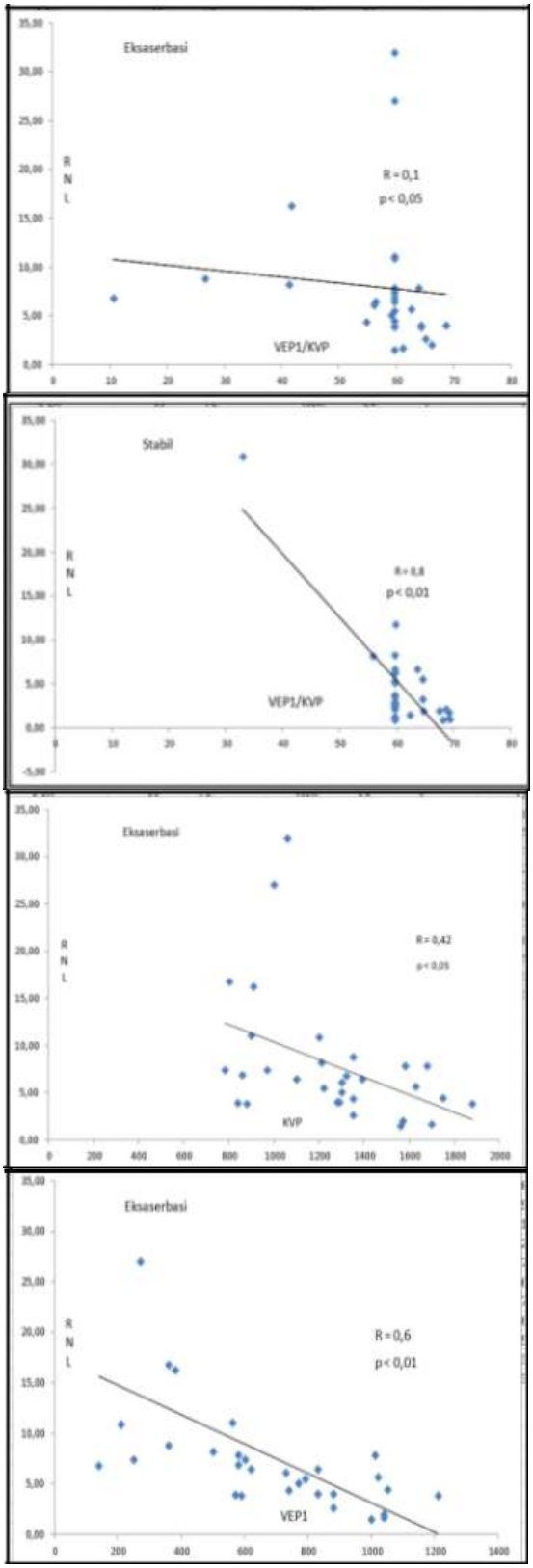
In AE-COPD, the NLR average was 7.95±6.8, while at stable 4.6±5.5. A total of 28 patients showed a decrease in NLR

during stable conditions. Three patients showed a higher NLR in a stable condition. Meanwhile, CRP levels in 10 patients showed higher levels at stable condition than exacerbation. The CRP average in AE-COPD was 43.4±71, while the stable condition was 12.2 ± 18.5. The difference was statistically significant based on the Wilcoxon test (P<0.01). Graphic 2 shows the average difference between the two variables.



Graphic 3. A) Correlation between NLR and CRP values at exacerbation. B) Correlation between NLR and CRP at stable condition

The results of this study indicate that there is no correlation between NLR and CRP. Correlation data analysis was carried out with the Spearman correlation test for quantitative data with a non-normal distribution. In addition, the NLR and CRP values shown in Graphic 3A were analyzed in an exacerbation condition.

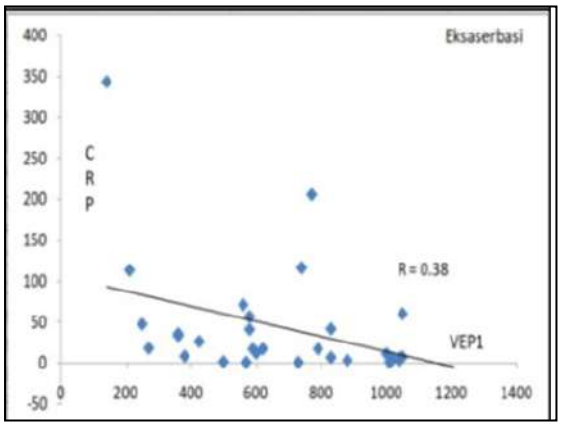


Graphic 4. Correlation of NLR with FVC and FEV1

The correlation between NLR and FVC and FEV_1 was analyzed using Spearman and found to have an inverse correlation

(negative). As in NLR with CRP, data processing of NLR and spirometry results were also based on exacerbation status. The correlation coefficient between NLR and FVC in AE-COPD and stable was r = -0.42 and r = -0.17, respectively.

NLR also showed a negative correlation with FEV_1. In AE-COPD, the value of the correlation coefficient r = -0.6 while in stable conditions is -0.54. Airway obstruction, as indicated by the FEV_1/FVC, also showed a negative correlation. The correlation coefficient value of NLR with FEV_1/FVC at exacerbation is r = -0.1 with P<0.05. In stable conditions, Spearman's analysis showed a significant correlation (r = -0.8; P<0.01).



Graph 5. Correlation between CRP value with FVC and FEV1

CRP also showed a negative correlation. In AE-COPD, there was no significant correlation between CRP and FVC with r = -0.04, while in the stable condition, it was -0.26. The correlation coefficient of CRP with FEV_1 in the exacAE-COPD and stable group was r = -0.38 and r = -0.27, respectively. There is no correlation between these two variables with FEV_1/FVC (r = -0.17) in the exacerbation condition (P=0.07) and r = -0.24 (P=0.3) in the stable condition.

The Spearman correlation test showed no correlation between CRP and CAT scores in both exacerbating and stable conditions. The correlation coefficient obtained was r = 0.17 (P=0.37) at exacerbation and r = 0.32 when stable with P=0.08. Similarly, NLR did not show a correlation with CAT.

There is no correlation between the CAT score and FEV_1/FVC in both exacerbated and stable condition. This study tends to find that the CAT score can change based on the exacerbation status in the same patient. In stable conditions, the CAT value was lower but not correlated with FEV_1/FVC. The correlation coefficient values of CAT with FEV_1/FVC in exacerbation and stable conditions were r = -0.28 (P=0.94) and r = -0.16 (P=0.37).

Based on the Spearman correlation analysis, the NLR and CRP in AE-COPD did not correlate with exacerbation incidence within 1 month after the last exacerbation. Seven patients (21%) experienced one relapse within one month after the previous exacerbation. The mean NLR of exacerbations of this one-time relapse was 5.7. As for CRP, the average level in patients who experience one recurrence in one month is 77.5.

Two patients died after data collection. The patient died within one month of completing data collection. One patient who died recorded his NLR and CRP in AE-COPD 3.8 and 17, while when stable, they decreased to 2.1 and 6.3. The other patients showed NLR and CRP values of 6.8

and 343.9 (AE-COPD) while those stable were 11.7 and 94.7, respectively. The first patient died with a history of no improvement in high pCO_2 on blood gas analysis. Meanwhile, the other patients had no known history of the cause of death. The increase in NLR when stable was shown by patients who died above and other patients, from 2.61 at exacerbation to 6.2 when stable. In contrast to patients who died, the CRP value in these patients decreased from 3.1 to 0.5.

This patient was known to have experienced 1 exacerbation in one month after examining a stable condition. There were three patients with higher CRP in stable, experiencing exacerbations within one month after the regular period, with one case requiring treatment in the intensive care unit for indications of type 2 respiratory failure.

The other seven patients had no exacerbations within one month. The mean CRP of these patients was 3.3, while the three patients who had exacerbations returned, showing a mean CRP of 14.3 at the time of the previous exacerbation. One patient showed a high CRP value of 205.8 at the time of exacerbation. This patient had no recurrence of exacerbations within one month of the worsening. The patient showed a drastic decrease in CRP, which was down to 9.8 in a stable condition. Patients with higher CRP values, when stable, who experienced a recurrence of exacerbations within one month were not accompanied by an increase in NLR while stable.

The GOLD criteria were made based on the patient's spirometry results while in stable condition. Therefore, the difference in mean shows an increase as the GOLD criteria increase. However, as previously explained, the number of patients in each group of GOLD criteria was not balanced. There were no patients on GOLD IV, and there was only one patient on GOLD I. Statistically, the mean difference that was significant was only indicated by the CRP value. The patient is in stable condition.

DISCUSSION

Former smokers dominated patients in this study with severe Brinkmann Index scores. This background is a risk factors for COPD. Some patients met the criteria for COPD GOLD II.

CAT scores decreased when conditions were stable compared with exacerbations in the same individual. It is known that the value obtained from the CAT score is an important part of COPD patients' management. A Japanese study conducted by Suetomo in 2014 that focused on studying whether CAT could be used to predict exacerbations in COPD patients showed that CAT could predict exacerbations. However, this study did not find evidence that CAT can indicate the need for hospitalization in COPD patients because not all COPD patients who experience exacerbations are hospitalized. It is said that the intention of the CAT to facilitate communication between doctors and patients regarding

the effects of a disease that occurs in patients with COPD.[12]

Another study conducted by Ghobadi in 2011 concluded that the CAT score is closely related to the severity of airway obstruction.[13] However, the results mean as in the study was not found in this study. There are two elements in the CAT assessment, namely respiratory and non-respiratory symptoms.[14] In this study, the patients' improvements in the CAT score varied.

This study showed that the NLR of AE-COPD patients was significantly higher. Considered the GOLD criteria, the NLR value in stable condition shows an average difference. The NLR mean of GOLD II and III in AE-COPD was 6.24 and 14.74, respectively. Meanwhile, in stable patients 3.7 and 8.7. In GOLD I group, there was only one patient and this patient had an NLR of16.75 (AE-COPD) and 5.14 when stable.

A previous study conducted in Japan (2011) by Furutate et al. found an increase in NLR value as the degree of airway obstruction worsened. In this study, the increase could be in line with the rise in GOLD criteria. The result of this study showed a similar trend, but the patient number of each subject was not balanced. Considering this fact, the suitability of the increase in NLR with the degree of airway obstruction could not be further assessed. Nevertheless, the analysis of the difference in mean NLR between the GOLD groups showed a statistically significant difference ($P<0.05$) in both exacerbation and stable conditions.[9]

It is known based on the GOLD guidelines that FEV_1/FVC below 70% post-bronchodilator is a criterion for establishing a COPD diagnosis. This value also describes the severity of airway obstruction. In contrast to the explanation in the previous paragraph regarding NLR and the GOLD criteria, the correlation test between NLR and FEV_1/FVC showed a significant correlation. From Graphic 4, NLR is negatively correlated with FEV_1/FVC in both AE-COPD and stable. These results are consistent with previous studies, which consistently found that high NLR was associated with decreased lung function. In contrast to the analysis of prior studies, this study distinguishes between exacerbation and stable analysis.

Research by Xiong et al. in 2017 also found a significant correlation between NLR and COPD severity. Xiong analyzed prognostic factors and concluded that NLR was correlated with mortality. In contrast to the objectives of this study, this study did not aim to find a correlation between NLR and mortality.[5] However, two patients died after the study was completed. One of the patients who died showed increased NLR when they were stable. It can be argued that this case supports Xiong's finding that NLR may be a predictor of mortality in COPD patients.

In 2015, Lee et al. obtained results showing that the NLR value of 2.8 is the limit value for predicting the risk of

hospitalization caused by exacerbations in COPD patients.[6] These results are consistent with this study, which obtained an average NLR of 7.95 in AE-COPD requiring hospitalization. The theory states that COPD is a persistent systemic inflammatory disease. This study did not involve healthy patients as controls, but there was a clear difference in the NLR mean during stable versus exacerbation conditions in the same individual.

Several mechanisms may explain the increased systemic inflammation in COPD. The first possibility is the spillover of inflammatory mediators from the pulmonary compartment. In addition, another possibility is in response to the presence of tissue hypoxia. It is known that COPD patients experience tissue hypoxia on average due to insufficient respiratory conditions. The third possibility is caused by the immune system's response to bacterial infections that cause COPD exacerbations. For example, for gram-negative bacteria, the lipopolysaccharide (LPS) component of these bacteria will be recognized by TLR-4 on the surface of innate immune cells as antigens.[7]

Furthermore, proinflammatory pathway activation will produce cytokines and chemokines to recruit more immune cells, including neutrophils and lymphocytes. Neutrophils are increased in COPD patients who experience exacerbations due to bacterial infection, but this does not mean that bacterial infection is the only cause of increased neutrophil levels.[7]

The deficiency of alpha-1 antitrypsin is a risk factor for developing COPD in a person. Still, because this case is considered as rare, especially in Asian races, neutrophils are the cause of an imbalance between proteases and antiproteases in the lungs. Neutrophils recruited to the walls of the airways and lungs as an innate immune cell reaction to infection will produce oxygen radicals and proteolytic enzymes such as proteases, causing tissue damage. This pathophysiology describes the emphysematous type of COPD. Likewise, in chronic bronchitis, several studies that focus on the analysis of airway smooth muscle have shown a relationship between the degree of neutrophil infiltration and the severity of airway obstruction.[7,15]

Discussion of lymphocytes, which are components of NLR, has been shown by several studies that found infectious pathogens were the background for the increase in lymphocytes in patients. Most of the $CD8^+$ T lymphocytes in patients with COPD are versions of memory T lymphocytes. It means that in COPD patients, there has been the introduction of infecting pathogenic bacteria that produce $CD8^+$ T lymphocytes in T cell differentiation and then produce memory T cells as one of the differentiation process results. Memory $CD8^+$ T lymphocytes will then respond very quickly to infecting bacteria in subsequent infections, and this response is the background for exacerbations and other immune components.[15]

High lymphocyte counts in stable COPD patients may have two meanings: as a result of previous exacerbations and as an indication of the immune system "understanding" and "responding" that a person's respiratory system needs more protection.[15] Low lymphocyte count or lymphopenia in some cases of infection such as sepsis, bacteremia, and some chronic diseases such as cardiovascular disease and cancer are associated with a poor prognosis. In some COPD patients, lymphopenia is associated with advanced age and poor nutritional status.[8]

There is a postulate from Xiong et al.'s study that NLR, which integrates neutrophils and lymphocytes, shows more association with COPD than neutrophils or lymphocytes alone.[5] A high NLR value, which means neutrophilia and lymphopenia together, indicates inflammation and a decreased immunity, as well as non-optimal health conditions. This is following COPD's essence, a systemic inflammatory and immunocompromised condition.

Three patients in this study showed a higher NLR in stable condition compared to exacerbation. In addition, the patient showed a stable condition of lymphopenia, resulting in a higher neutrophil to lymphocyte ratio value. This is related to age and poor nutritional status. The three patients were aged 75, 81, and 66, respectively with a body mass index of 16,17 and 21. Some of these results show agreement with the theory that lymphopenia in COPD can occur in geriatrics and poor nutritional status. For example, when the condition was stable, one of the five patients with high NLR values was 81 years old with a BMI of 17.

This study also observed the CRP levels of COPD patients. The average CRP in AE-COPD was much higher than stable. High CRP levels are inversely correlated with airway obstruction. This study found that FEV_1 is associated with NLR, but no correlation was found between NLR and CRP. Related to the basic theory of neutrophil recruitment by proinflammatory cytokines, this result is not representative.

The ratio of neutrophils to lymphocytes consists of two important components in inflammation: neutrophils and lymphocytes. High levels of NLR can indicate the number of neutrophils in the blood, which is a continuation response of Interleukin (IL)-8 produced by innate immune cells. Interleukin (IL)-8 is a cytokine and chemokine that is produced together with other innate pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-12, and TNF-alpha. Neutrophils have a direct relationship with IL-8, as well as IL-6. Furthermore, hepatocytes produce CRP in response to IL-6, which is captured by hepatocyte receptors.[11] Theoretically, this indicates that the CRP value should be in line with the NLR, but this was not found to be the case in this study. Although NLR and CRP together showed a decrease in levels when the condition was stable, some patients experienced an increase in CRP in stable condition, not including those who also experienced an increase in NLR

when stable. The analysis results that do not show a correlation can be caused by this explanation.

Another factor is that some patients who showed high NLR have lymphopenia, therefore the NLR count results are high. This could be due to the low number of proinflammatory cytokines produced by innate immune cells, including IL-6 cytokines, resulting in NLR and CRP values obtained did not show a correlation. In patients who show a high NLR with lymphopenia condition, there are not many neutrophils, so there are few proteases. As a result, tissue damage can be a stimulus for the production of proinflammatory cytokines. In this case, the not-so-much IL-6 is followed by low CRP, which causes a weak correlation between NLR and CRP in the overall analysis.

The absence of CRP and NLR correlations obtained from this study, although not by previous studies, actually shows the line with theory regarding the pathophysiology of CRP production by the liver. Infection can be caused by a variety of infectious agents other than bacteria. An example is a virus. The incidence of viral infections in the respiratory tract that can cause acute exacerbations in patients with COPD is quite high.[16]

In this regard, the effect of CRP produced by the liver may be different from that of produced due to bacterial infection. The theory shows that virus infection will result in a low CRP value, while a bacterial infection will cause a significant increase in CRP.

The pathways of immunological responses to bacteria and viruses differ from one another. As mentioned above, macrophages will respond first by phagocytosis and producing proinflammatory cytokines in response to bacterial infections. Among several proinflammatory cytokines, there is IL-6 which will be captured by receptors on hepatocytes, followed by the production of CRP by the liver. The process is different in conditions of viral infection. Interferon (IFN) is a proinflammatory cytokine predominantly produced in response to viral infection. This interferon-dominated immunological response could be the background for the low CRP produced by hepatocytes even though it is still produced as an inflammatory response.

This background may be the reason for the lack of a correlation between NLR and CRP in this study. The causes of exacerbations were not examined further, resulting in a not-known cause of exacerbation (by bacteria or viruses). A significant increase in CRP in some patients might be caused by a bacterial infection, while a virus infection can cause a small increase in CRP. In the previous discussion, it was mentioned that there is a possible correlation between high NLR counts due to lymphopenia and age and nutritional status.[8]

In this study, it was also found that patients who showed high CRP values in stable conditions had a BMI below normal with a mean of 18.4. This result is lower than patients who showed decreased CRP

in a stable condition: 21. In addition, CRP levels showed an inverse correlation with FEV_1, which is an inverse correlation. These results indicate that the consequences of COPD are not only directed toward towards the respiratory system but also extrapulmonary and systemic.

This result is interesting because COPD is a chronic inflammatory condition, while CRP is an acute-phase protein produced by hepatocytes in response to inflammation or tissue damage. The study conducted by Gan et al. is the first to derive significant value from high levels of CRP in COPD patients. The study showed that the results of CRP increased in active smokers, patients with decreased lung function, stable COPD patients, and even high levels of CRP were predictors of mortality related to cardiovascular disease.[16]

Other studies have shown that patients with COPD have higher CRP levels, which is not associated with cardiovascular disease. However, it was also found that CRP can predict mortality in COPD patients, and CRP levels can decrease with routine exercise.[17–19]

The study by Furutate et al. found a strong correlation between CRP and NLR in COPD patients, but the study did not mention the possibility of CRP as a predictor of mortality in COPD.[9] Meanwhile, Yousef said that NLR was more likely to represent exacerbations in COPD patients than other inflammatory markers such as CRP.[20] In this study, there are several noteworthy findings regarding the usefulness of both NLR and CRP. Two patients in this study died, and one showed very high CRP levels (>300) at the time of exacerbation.

In this case, although CRP levels decreased when stable within one month later, the levels were still far above the normal value. Simultaneously, these patients also showed an increased NLR when stable compared to exacerbations. Other patients who died also showed CRP levels decreased when stable but remained above the maximum reference value. In contrast to the previous death case, this one was not accompanied by an increase in NLR. Meanwhile, the correlation test from this study did not show a correlation between CRP and the frequency of exacerbations within one month.

Several CRP values which showed an increase when stable compared to exacerbations showed a possible correlation with exacerbation recurrence within one month. Interestingly, there are some patients with an increase in CRP when stable, but the CRP value was not too high during the previous exacerbation, did not experience a recurrence of exacerbation within one month. Likewise, the finding that an increase in NLR does not accompany an increase in CRP does not show an association with death in COPD patients. It is important data and may be used as the basis for further research to explore the possibility of NLR and CRP as predictors of mortality in COPD patients at Persahabatan Hospital.

This study has limitations, including not including healthy people without COPD as the control group. In addition, in this study, the number of samples in each GOLD group was not balanced. This is the reason for the inconsistent increase in NLR and CRP and the increase in the GOLD criteria. The cause of the exacerbation in this study was also not examined further, whether it was a bacterial or viral infection. It affects the various increases in CRP. Another limitation of this study was that not all patients could prove the use of inhaled drugs within the framework of COPD treatment correctly because some patients did not take their medication with them at the time of the examination. It may be a confounding variable in this study.

CONCLUSION

NLR values in COPD patients were higher in exacerbation conditions than in stable conditions. The NLR value showed an inverse correlation with FEV_1, FVC, and FEV_1/FVC only in exacerbation conditions in COPD patients. There is no correlation between NLR scores and CAT scores in COPD patients. There is no correlation between NLR and CRP values.

Further research is needed to include healthy people without COPD, smokers and non-smokers to determine the NLR and CRP values. In addition, it is necessary to conduct a study with a balanced number of patients on each of the GOLD criteria. Another thing that adds to further research is the classification of causes of exacerbations, such as bacterial infections, viruses or other causes. The high CRP value in this study indicates a possible correlation with exacerbations and mortality, but this is not included in the purpose of this study. But this evidence can be the basis for further research to focus more on CRP as a predictor of recurrence and mortality in COPD.

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Case Report

Multiple Possible Causes of Dyspnea in An Unusual Pickwickian Syndrome In The COVID-19 Pandemic: A Case Study

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Abstract

Pickwickian Syndrome (PS) or obesity hypoventilation syndrome (OHS) is a diagnosis of exclusion with features of obesity, sleep disordered breathing, and chronic daytime hypercapnia. Patients with PS may exhibit general OSA or respiratory failure. We present an unusual case of PS with acute respiratory failure, which resulted in organ failure and death. A 41-year-old male was admitted to the hospital due to shortness of breath. He had sleeping trouble, frequently awaking as the breathing briefly stopped and gasped. There was a history of diabetes melitus (DM) and hypertension for more than ten years, as well as smoking with a moderate Brinkman Index. The patient appeared to be drowsy, tachypneic, hypoxic, and morbidly obese. We diagnosed him with PS, bronchopneumonia, respiratory failure, pulmonary edema, hypertensive heart disease (HHD), DM, acute on CKD. We treated him with medication, oxygen therapy (BiPAP), and hemodialysis. After being transferred from the ICU to the general ward, the patient became apneic and CPR was attempted; nonetheless, the patient died. This unusual case (malignant OHS) was a subgroup of OHS with greater morbidity and multiorgan system dysfunction. There were multiple causes of dyspnea in our patient, which concluded to be a death case. There are three modalities of management for stable PS: positive airway pressure (PAP), weight reduction, and pharmacotherapy. The treatment of respiratory failure in PS was primarily accomplished through the use of positive pressure oxygen therapy. There were multiple causes of dyspnea in this patient. For optimal management, not only should the PS be treated, but other comorbidities should be addressed as well.

Keywords: pickwickian syndrome, malignant obesity hypoventilation syndrome

INTRODUCTION

The term 'Pickwickian Syndrome' was first popularized by a case report from Burwell et al based on the same description of one character in Charles Dickens' *The Posthumous Papers of the Pickwick Club,* whom the author referred to as "Joe", a fat boy who is always asleep and has a very

extraordinary degree of somnolence.[1,2]

Obesity Hypoventilation Syndrome (OHS), also known as Pickwickian Syndrome (PS), is a diagnosis of exclusion with features of obesity (body mass index/BMI $\geq$30 kg/m^2), sleep disordered breathing, and chronic daytime hypercapnia ($PaCO_2$ $\geq$45 mmHg), with no other causes of hypoventilation or hypercapnia (obstructive airway disease, interstitial lung disease, neuromuscular disease, metabolic-severe hypothyroidism, or chest wall disease-kyphoscoliosis). Almost 90% of OHS patients have obstructive sleep apnea (OSA). However, the presence of OSA is not necessary for the diagnosis of OHS (no need for polysomnography).[3–5] The remaining 10% of OHS patients have sleep hypoventilation, which is described as having oxygen desaturation during sleep unexplained by obstructive apneas or hypopneas.[6]

According to the 2018 Basic Health Research from the Ministry of Health, Republic of Indonesia, the proportion of obese people (BMI $\geq$27 kg/m^2) in the Indonesian population has increased from 10.5% in 2007 to 21.8% in 2018.[7] Unfortunately, the prevalence of OHS is unknown in Indonesia as well as in other countries. Nevertheless, the OHS prevalence can be estimated at 0.15 to 0.3% in the United States (more prevalent than in other nations due to the obesity epidemic).[5] Patients with OHS may present in two ways, each with its own set of medical help routes: as part of the general OSA population or with rapid deterioration leading to severe respiratory failure (requiring intensive care).[8]

A study by Rasmin et al in Indonesia pointed out that among patients who presented with acute respiratory failure, 44.7% were hypercapnic and about 13.6% had acute on chronic respiratory failure. However, there was no data regarding acute respiratory failure due to OHS in Indonesia.[9] We are presenting an unusual case of Pickwickian Syndrome with signs of acute hypercapnic respiratory failure (AHRF) and multiple possible causes of dyspnea, all of which resulted in organ failure and death.

CASE REPORT

A 41-year-old Indonesian male was admitted to the hospital due to shortness of breath aggravated by physical activity that started 2 days before admission. The breathlessness was also intensified by position (orthopnea). There was no cough, wheezing, chest pain/discomfort, or fever. Nutritional intake was admitted to be exceptional. Approximately 9 months ago, the patient was hospitalized in another hospital for a same chief complaint and spent 13 days in the ICU.

At the previous hospitalization, the record of chest X-ray (CXR) showed pulmonary edema and the laboratory results indicated renal failure (suspected acute on chronic kidney disease) and mild hypoxemia with compensated chronic respiratory failure from blood gas analysis. The spouse mentioned that this patient

demanded a very huge portion of rice per meal served and that it had been such for a long period of time. She also stated that her husband had sleeping trouble, that was, snoring, could not sleep soundly; frequently awoke as the breathing briefly stopped and gasped.

The latter was neither treated nor diminished after the last hospitalization and was repeatedly observed during this period of inpatient care. The patient had a history of diabetes melitus and hypertension for >10 years, consumed 10 mg of amlodipine once daily and also a combination of 500 mg of metformin and 2 mg of glimepiride twice a day. He had a moderate Brinkmann Index with a history of 25 years of cigarette smoking, 12 cigarettes per day.

The physical examination showed a severely-ill general condition, indicated by somnolence, blood pressure of 179/125 mmHg, heart rate of 116 bpm, respiratory rate of 28/min with rapid and shallow breathing, and peripheral oxygen saturation of 67% in room air (escalated to 93% after O_2 supplementation using a non-rebreathing mask/NRM). The temperature was within the normal range. Upon observation, there were periods of snoring and gasping during the first hour in the emergency department (ED).

The patient was morbidly obese with a BMI of 56.64 kg/m^2 (body weight 145 kg and height 160 cm). In the neck area, there was a thick layer of subcutaneous fat that made it difficult to do a neck examination (jugular vein pressure, presence of lymphadenopathy, and tracheal palpation). Pulmonary examination revealed dull percussion on both hemithorax bases and rales on auscultation, as well as wheezing and prolonged expiration. Heart sounds were regular. Both legs were swollen.

Furthermore, as we were still in the COVID-19 pandemic and the patient had acute dyspnea, we did a swab test as screening. The antigen swab test result was negative, confirmed by a negative SARS-CoV2 PCR test result. The patient was shortly consulted by the internist, pulmonologist, cardiologist, and intensivist, then immediately transferred to ICU after stabilization in the ED.

Arterial blood gas analysis (ABGA) showed AHRF with pH 7.104, $PaCO_2$ of 117 mmHg, PaO_2 of 53.9 mmHg, HCO_3 of 35.9 mmol/L, normal base excess, and O_2 saturation of 84.5%. Other lab tests were: normal Hb (17 g/dL) and hematocrit (52%), leukocytosis (16,700/µL) with an increased Neutrophil-Lymphocyte Ratio (NLR) of 9.11, normal blood glucose with an increased HbA1c (8.2%), normal liver function but impaired kidney function (ureum of 65 mg/dL, creatinine of 3.30 mg/dL with an estimated glomerular filtration rate/eGFR of 22.1 mL/min/1.73 m^2 and uric acid of 12.4).

Urinalysis indicated proteinuria, glucosuria, and hematuria. The electrocardiography (ECG) showed regular/sinus rhythm, RBBB, with no signs of hypertrophy, ischemic or infarction. The CXR (Figure 1) showed cardiomegaly and

pulmonary edema while echocardiography showed normal ejection fraction (71%) and LVH. Chest CT scan (Figure 2) indicated cardiomegaly with pulmonary vascular congestion, pulmonary edema and pneumonia.

We assessed the patient as having OHS, bronchopneumonia, type 2 DM, hypertensive heart disease (HHD), and acute on chronic renal failure (acute on CKD) with AHRF, low chest expansion, acute pulmonary edema, immobilization, and uncontrolled blood glucose. We managed the patient with oxygen support (positive pressure) and aminophylline (respiratory stimulant) for the AHRF, an antibiotic for pneumonia, insulin to regulate the blood glucose, diuretics and anti-hypertensive drugs for the pulmonary edema and HHD.

In the ICU, we used non-invasive ventilation (NIV) with BiPAP mode (P_{insp} 10 cm H_2O, PEEP 8 cm H_2O, FiO_2 50%) and did chest physiotherapy to overcome the AHRF. The patient had good clinical responses toward the treatments given, marked by improvements in symptoms, consciousness and vital signs. Nevertheless, the pulmonary auscultation pointed out otherwise. Weaning of NIV was then made from BiPAP to CPAP mode following a better ABGA result taken the day after NIV administration (pH 7.281, $PaCO_2$ of 64.2 mmHg and PaO_2 of 83.1 mmHg).

During the observation, we found daily fluid balance was always in positive trends with decreased urine output and finally reached a urine output of 80 mL per day. Worsening kidney function led to acute CKD being established as we looked for an etiology other than diabetic-hypertensive nephropathy. Following a consultation with the nephrologist, the decision was made to begin renal replacement therapy and hemodialysis on this patient. The initial hemodialysis successfully withdrew 1,000 mL and eventually created a negative fluid balance. Two days after, hemodialysis withdrew 2,384 mL, so the daily fluid balance was found to be negative only on days with a hemodialysis schedule. Getting more stable, the patient was then transferred to the regular ward. We had already arranged for plans to perform a spirometry and also to get this patient an NIV for nocturnal use after discharge.

However, 10 hours after being transferred to the regular ward, the patient was agitated and having air-hunger behavior. The spouse acknowledged that the patient leaned forward, tried to breathe, and suddenly took off his oxygen mask. She called the nurse, but unfortunately, the patient appeared apneic and cyanotic with no palpable carotid pulse. The team did cardio-pulmonary resuscitation for 30 minutes, but no response was obtained and he was declared dead.

DISCUSSION

The condition of our patient was complex. The diagnosis of OHS was

accompanied by some other comorbidities which had been experienced by our patients in the long term, most of which also had a role in generating dyspnea. This "unusual" case of Pickwickian Syndrome was mentioned in other studies or reports as "Malignant OHS" (MOHS).[10]

This MOHS is a subgroup among OHS patients with a higher BMI (>40 kg/m^2) that accounts for greater morbidity and multiorgan system dysfunction. As mentioned in the study by Marik and Desai about MOHS patients' characteristics, all of these patients were admitted to ICU due to AHRF, all had metabolic syndrome and high HbA1c. Some of these patients were also diagnosed with pneumonia, acute or chronic renal failure, sepsis, cellulitis, pulmonary hypertension, and nonalcoholic steatohepatitis (NASH).

From our point of view, there were some causes that possibly induced the symptom of dyspnea in our patient. Some should have been dominant, some were not. There were multiple possible causes of dyspnea in our patient that apparently concluded in a death case, such as OHS, AHRF, bronchopneumonia, acute pulmonary edema, HHD, and acute CKD, which will be individually discussed in the following paragraphs.[11]

Obesity Hypoventilation Syndrome and Acute Hypercapnic Respiratory Failure

Our patient met the features of OHS, which were obesity, sleep disordered breathing, and hypercapnia. Obesity in Indonesia applies a lower BMI cut-off point than in the US, that is >27 kg/m^2, while our patient was severely obese with a BMI of 56.64 kg/m^2. Sleep disordered breathing was also found in our patient, as mentioned by his spouse and observed during treatment in the ICU. Although our patient had a history of smoking with a moderate Brinkman Index (a risk factor of COPD), the diagnosis of acute respiratory failure was mostly led to OHS because such a feature of sleep disordered breathing was commonly absent in COPD.

Diagnosing a potential coexisting COPD from smoking habit in this patient should have been difficult, so spirometry was already planned whenever the patient was stable in an out-patient setting, but the patient died.Marik in a large cohort study of OHS patients revealed that about 43% of OHS patients had been erroneously diagnosed as having COPD.[12] Therefore, the diagnosis of COPD in an OHS patient should be made with caution.

It was quite difficult to demonstrate the presence of daytime chronic hypercapnia in our patient as he was admitted with AHRF, shown by the ABGA with a very high level of PaCO2, mild hypoxemia, and an elevated bicarbonate level. However, elevated bicarbonate levels as a metabolic compensation for respiratory acidosis are quite common in OHS and indicate the chronic nature of hypercapnia. The Hb and hematocrit levels also attained nearly the upper normal limit. There we could see signs of acute and chronic respiratory failure, indicating

intensive treatment. The alveolar to arterial oxygen gradient ($AaDO_2$) from the admission ABGA was calculated to be 566.75 mmHg (FiO_2 of 100%). We considered elevated $PaCO_2$ with high $AaDO_2$ as signs of hypoventilation, along with another mechanism of hypoxia, that was either a shunt or a V/Q mismatch. As the patient responded well to the NIV and the evaluation of ABGA indicated a correctable PO_2, then the hypoxia was produced by the V/Q mismatch.[5]

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Patients with OHS have respiratory abnormalities originating from three interacting sources: alteration of pulmonary function related to obesity, changes in central ventilatory drive, and sleep disordered breathing. Obesity in OHS causes more significant changes in reduced lung volumes (total lung capacity/TLC, functional residual capacity/FRC, expiratory reserve volume/ERV, vital capacity/VC, and forced expiratory volume in one second/FEV_1) than eucapnic morbidly obese patients. Excess fat deposits in the abdomen, chest wall, and diaphragm may reduce the chest wall and lung compliance aside from decreasing lung volume. Breathing at low lung volumes enhances airway resistance due to small airway closure during exhalation in both sitting and lying positions. All of these, with associated respiratory muscle weakness, increase the work of breathing and if the patient is unable to compensate with elevated ventilatory drive, then OHS occurs.[4,13,14]

The comparison of excess fat deposits on the chest wall and the size of the lungs of our patient can be seen in Figure 2, while the exact objective measurements of lung volumes and capacities from spirometry were not fulfilled. By observing the comparison between excess fat on the chest wall and the lung sizes of our patient, we were assured that restrictive disorder should have taken place from the very beginning of the patient's respiratory problem.[4,13,14]

The majority of morbidly obese patients who maintain eucapnia have intensified respiratory drive as a compensation for abnormal respiratory workload (due to fat deposition). This can be observed similarly to normal subjects whose chest walls are loaded with something heavy. Obese subjects have escalated rates of oxygen consumption and carbon dioxide production; therefore, they have to accelerate minute ventilation

for compensation. If they fail to meet this compensation due to blunting hypercapnic and hypoxemic ventilatory responsiveness, then they could develop hypoventilation and OHS.[4,13,14]

The origin of this blunting response is hypothesized to be a consequence of some causes, namely obesity, genetic predisposition, sleep-disordered breathing, and leptin resistance.[5] Leptin, an adipokine that supresses appetite, acts on central respiratory pathways as a powerful stimulant to augment ventilation. However, there is increasing evidence that leptin resistance could promote OHS.[13]

Central resistance to leptin (from persistent obesity) may lead to alteration of ventilatory control and deterioration of compensatory mechanisms to increased respiratory workload, culminating in OHS. Chronic hypoxemia and hypercapnia predispose OHS patients to pulmonary hypertension and secondary erythrocytosis.[13]

The latter was found in our patient, as shown in the full blood count result. We believe that leptin resistance has already taken place in our patient, as referred to by a clue gained from the alloanamnesis of the spouse, who confessed that our patient demanded a very huge portion of rice per meal served (high in calories and carbohydrates) and that it has been so for a long period of time. This was a sign of leptin resistance as the suppression of appettite did not occur normally. Hence, ventilatory control was also altered and OHS was sustained.

Obese subjects have altered physiological conditions on supine sleep. Significant upper airway narrowing is linked to excessive fat depositions surrounding upper airway and nocturnal fluid shift from the lower extremities (fluid overload and edema in the obese) to the neck. Both causes decrease pharyngeal size and promote collapsibility. This narrowing or closure of upper airway contributes to obstructive events during supine sleep. Same matter also applies to OHS patients, where they experience long-lasting apneas and hypopneas with insufficient ventilatory compensation owing to reduced control from the respiratory centres.[4]

It leads to a significantly greater oxygen desaturation on apnea episodes compared to obese eucapnic patients. Recurrent nocturnal hypoxemia elevates arousal threshold then may blunt the hypoxemic ventilatory response and conclude to hypoventilation.[13] Likewise, blunted hypercapnic ventilatory response occurs if compensation for acute CO_2 loading was diminished which gave a progressive rise in $PaCO_2$, accompanied with compensatory renal bicarbonate retention. Daytime hypercapnia due to obstructed nocturnal breathing develops when appropriate ventilatory and renal compensatory response are compromised.[14]

Our patient had a very thick fat deposits on his neck, generating difficulty in examining neck area and also producing

obstacle if tracheostomy is indicated for him. His legs were also swelling, therefore we never put him on supine position to minimize the worsening of sleep disordered breathing. Sleep disordered breathing on our patient was observed during treatment in ICU in the form of sudden choking or gasping. As stated before, OHS could be diagnosed either when a patient reaches an acute-on-chronic exacerbation with acute respiratory acidosis, leading to admission to the ICU, or during a routine out-patient evaluation by a pulmonologist or sleep specialist.[4] A study from Marik pointed out that 63% of OHS patients were hospitalized with an admission diagnosis of respiratory failure.[12]

Chebib et al. stated that about 32.1% of OHS patients (37 out of 115) in their study were admitted to the ICU for AHRF.[15] There was no exact data in Indonesia regarding AHRF that emerged from OHS. The only Indonesian data on acute respiratory failure was studied by Rasmin et al., who pointed out comparable proportions of hypoxemic (55.3%) and hypercapnic (44.7%) acute respiratory failure, with pneumonia as the most common cause (58.7%) of acute respiratory failure.[9] Our patient was admitted for strict monitoring and treatment in the ICU due to AHRF and other diagnoses.

Bronchopneumonia and Screening for COVID-19

Our patient also had pneumonia based on the clinical symptoms, physical examination, and chest CT. Dyspnea, or breathing discomfort, is one of several symptoms of pneumonia. Seeing that we are still in a COVID-19 pandemic and the chest CT indicated signs of pneumonia (even though it was not specific for viral pneumonia), we carried out evaluation for COVID-19 from antigen swab and isothermal PCR swab; both results were negative. Strausz et al. identified that OSA was associated as a risk factor for severe COVID-19 manifestation (OR=2.37) besides other already identified-risk factors such as older age, male sex, obesity, diabetes, cardiovascular disease, and poor lung function.[16]

Our patient might already have at least 5 of those severe COVID-19 risk factors mentioned. Luckily, he was tested negative for COVID-19. The pneumonia seemed to be of bacterial origin and responded well to antibiotics, as seen in the reduction of leukocyte number (12,200/µL) three days after the antibiotic was administered. Pneumonia was found as an admission diagnosis in 20% of patients with OHS and 15% of MOHS.[11,12] Pneumonia was also reported as a complication in a third of all cases of acute renal failure (ARF).[17]

Hypertensive Heart Disease and Type 2 DM

Patients with OHS should already have comorbidities. Cardiometabolic comorbidities compromise the outcome of OHS patients and certainly cause dyspnea. Some of those comorbidities were found in

our patient, namely hypertension (HHD) and type 2 DM. The prevalence of essential hypertension in OHS patients ranged from 55–58%, while half of the OHS patients had pulmonary hypertension.[4] In a study comparing OHS patients with obese and OSA patients, Basoglu discovered that the rates of cardiometabolic comorbidities were higher in OHS patients, such as coronary artery disease (20.3% vs 15.3%), congestive heart failure (15.3% vs 10.2%), hypertension (67.8% vs 53.2%), and diabetes mellitus (35.6% vs 25.1%).[18]

A study by Castro-Aón et al also confirmed that OHS patients had higher BMI and more frequent histories of arterial hypertension, heart failure, and arrhythmia than OSAS patients, significantly. Patients with OHS had twice the risk of mortality and almost twice the risk of cardiovascular events than those of OSAS patients.[19] Patients with OHS tended to have more impaired endothelial dysfunction, which led to atherosclerosis and cardiovascular events. This was due to higher C-reactive protein (CRP) levels and a lower level of adiponectin, an antiatherogenic and insulin-sensitizing adipokine. Obesity causes low-grade chronic systemic inflammation and inflammatory changes in adipose tissue.[20]

In a previous study by Chebib et al, 54% of patients with OHS had congestive heart failure as the leading cause of AHRF for ICU admission in 54% of patients.[15] Our patient had a history of hypertension for more than 10 years with signs of congestive heart failure due to hypertensive heart disease as seen radiologically by the size of the heart (cardiomegaly), congestion of the pulmonary vasculatures and LVH on echocardiography. Edema on the legs was also observed. This could be compelling evidence that hypertension in our patient was uncontrolled, yet the medication all this time might also be neither adhered nor optimal.[4,21]

However, blood pressure was observed to be stable and respond to treatments given. It was fortunate that no signs of coronary artery disease or arrhythmias were found during monitoring in the ICU, but the sudden agitation and declines in vital signs of our patient in the regular ward were considered to be of heart attack origin. Compared with patients with eucapnic OSA and similar BMI, patients with OHS are more prone to manifesting cor pulmonale and pulmonary hypertension (PH).[4,21]

Almeneessier revealed that the prevalence of PH was in the range of 59% to 88% among OHS.[21] A study conducted to evaluate echocardiography and ECG in OHS patients emphasized that the prevalence of LV systolic and diastolic dysfunction was 25% and 60%, respectively, with 61.5% of them having normal ejection fraction. The prevalence of RV dysfunction and PH was 63.3% and 52%, respectively.[22]

Isolated nocturnal hypoxemia could establish permanent PH. Both pulmonary vasoconstriction and pulmonary vascular bed remodelling in the alveolar hypoxia of

OHS rendered PH the same way as COPD.[23] Either HHD or PH/cor pulmonale might produce dyspnea. According to the echocardiography result, we concluded that our patient had LVH with normal ejection fraction and no cor pulmonale or PH were inspected, so HHD was thought to be the cardiogenic cause of dyspnea in him.

OSA causes insulin resistance (lower insulin sensitivity and higher fasting insulin levels) as well as an increase in gluconeogenesis (higher levels of epinephrine, norepinephrine, and cortisol). Insulin resistance in OSA is also related to elevated CRP, TNF-a, and IL-6.[24] Intermittent hypoxia, which corresponds to obesity, leads to sympathetic activation, chronic inflammation, and oxidative stress, which bring about a reduction of insulin sensitivity, augmentation of gluconeogenesis, and beta cell dysfunction (decrement of insulin secretion). Intermittent hypoxia is also involved in lowered glucose uptake by the muscles, altered gut microbiota, and leptin resistance. All of these give rise to insulin resistance and glucose intolerance (type 2 DM).[25] This insulin resistance in OSA is not only noticed in obese subjects but also in non-obese subjects.[26]

Furthermore, patients with OHS demonstrated higher resistance to insulin and a higher level of glycated Hb.[20] Despite the fact that CPAP (continuous positive airway pressure) has been shown to reduce intermittent hypoxia and inflammatory markers in OSA and OHS, some meta-analysis studies concluded that CPAP had no place in significantly correcting HbA1c and fasting glucose, but may improve insulin sensitivity.[27–29]

Most studies pointed out that the prevalence of DM was higher in OHS than in OSA.[18,19,30] Our patient had a history of type 2 DM for more than 10 years without any history of insulin application. The HbA1c level was high and appeared to be higher than the previous hospitalization (9 months ago, HbA1c=6.0%), indicating uncontrolled blood glucose caused by either treatment non-compliance (irregular use) or suboptimal treatment (combination of oral hypoglycemic medications when insulin might already be indicated).Chronic intermittent hypoxia and leptin resistance (escalated appetite) had a role in insulin resistance in our patient that concluded he had type 2 DM. Furthermore, it had already occurred more than 10 years ago. Although type 2 DM may cause dyspnea if metabolic acidosis occurs and triggers the Kussmaul breathing pattern, nevertheless, the ABGA of our patient resulted only in respiratory acidosis.

Acute on Chronic Renal Failure and Acute Pulmonary Edema

Chronic kidney disease is described by the continuing presence of reduced kidney function. Obesity is associated with direct and indirect risk factors for CKD, some of which are major risk factors, namely type 2 DM and hypertension.[31] Overweight and obese individuals had a relative risk for developing CKD of 1.87 and

7.07, respectively, when compared to normoweight individuals. It was also thought that obesity was linked to CKD from hyperfiltration due to increased metabolic demands.[32] Sivam et al compared the prevalence of CKD in OHS and OSA. Stage 1-3 CKD was more frequently present in OHS (46%) than in OSA (22%).[31] The prevalence of CKD was higher among subjects with sleep-related breathing disorders (30.5%) compared to control subjects (9.1%).[33] Vice versa, sleep-related breathing disorders were also observed among CKD patients.[34]

Hypertension and type 2 DM, which our patient had had for more than 10 years, could bring many complications. In this topic, hypertensive nephropathy or diabetic nephropathy, Both lead to CKD through their complex pathogenesis. It can be considered so as he already had a record of worsening kidney function since the last hospitalization (9 months ago) but refused to have renal replacement therapy. Our patient was known to have CKD nine months ago and apparently had an acute deterioration of CKD, or so-called "superimposed ARF" (acute on chronic renal failure/ACRF).

Hsu et al defined superimposed ARF having both a peak inpatient serum creatinine greater than the last outpatient serum creatinine by >50% and receipt of acute dialysis.[35] Ali et al and Zhou et al described ACRF using the classification as follows:[36,37]

1. Risk (R-ACRF): serum creatinine level elevated by 50% or more from index serum creatinine but had not reached 350 µmol/L (3.96 mg/dL) or GFR reduced by 25% or more.
2. Injury (I-ACRF): serum creatinine level elevated by 100% or more from index serum creatinine but had not reached 350 µmol/L (3.96 mg/dL) or GFR reduced by 50% or more.
3. Failure: serum creatinine increased by 200% or more from index serum creatinine or serum creatinine had increased to 350 µmol/L (3.96 mg/dL) as recommended by Acute Dialysis Quality Initiative (ADQI) group.

In his previous hospitalization, our patient had a creatinine result of 2.5 mg/dL, and in this current hospitalization, the creatinine was 3.3 mg/dL with an eGFR of 22.1 mL/min/1.73 m^2 and even worsened to the level of 7.0 mg/dL with an eGFR of 9.1 mL/min/1.73 m^2 on 3 days. Our patient did have an elevated serum creatinine by >50%. We also performed dialysis to overcome the worsening creatinine and eGFR, and also to counterbalance the anuria (his urine output reached 80 mL per day).

Therefore, according to Hsu et al, our patient met the criteria of superimposed ARF. For the ADQI recommendation, our patient fulfilled the criteria of ACRF (failure). Acute chronic renal failure and/or fluid overload could produce dyspnea through non-cardiogenic pulmonary edema, which should be responsible for defective gas transfer in the alveoli in the form of a shunt.

Pulmonary edema that correlates with renal disease is generally classified as having secondary renal-cardiac consequences and primary renal/non-cardiogenic pulmonary edema. The latter corresponds to accumulation of excess extracellular fluid following impairment of water and solute excretion (fluid overload) or to increased pulmonary capillary permeability due to reduction of oncotic pressure in the plasma.[17]

In our patient, pulmonary edema was very evident on physical and radiological examination (CXR and chest CT). Fluid overload was also pronounced from daily fluid balance, which was frequently positive. Normal ejection fraction and LVH from echo portrayed cardiac compensation, so the pulmonary edema in our patient was mainly of primary renal origin (non-cardiogenic). As a result, daily fluid balance became negative only on the days when dialysis was scheduled, and clinical improvements became more apparent. By all means, the multimodal treatment combination for our patient brought about good progress until the unexpected abrupt decline in the regular ward.

Treatments: Three Modalities

There are three modalities of management in stable OHS patients: reversal of sleep-disordered breathing through positive airway pressure (PAP), weight reduction (medically or surgically), and pharmacotherapy (respiratory stimulants).[5,6,14] Treatment using PAP is recommended for medium to long-term use in either NIV or CPAP. The NIV uses bi-level pressure settings while CPAP has continuous pre-set pressure during the respiratory cycle to prevent obstructive apnea. The NIV provides additional ventilatory support, while CPAP enables carbon dioxide unloading.[4,5,38]

The effectiveness of CPAP is identical to that of NIV, but NIV is more costly and requires more resources and equipment training. Both were equally effective for correcting sleep hypoxemia, hypercapnia, gas exchange, daytime sleepiness, sleep quality, quality of life, and obstructive events (sleep disordered breathing). However, the use of each modality was not superior to the other and should be individualized for each patient.[4,5,38] In addition, both NIV and CPAP significantly reduced mortality in OHS and OSA patients at 5-to-10-year follow-up. The mortality rate in untreated OHS patients was higher than in treated OHS patients.[39]

The effectivity of weight loss through a comprehensive program (motivational counseling, diet and exercise) or bariatric surgery was described in a systematic review by Kakazu et al The comprehensive program reduced body weight but had no clinically significant effects, whilst bariatric surgery lowered more weight and was correlated with improvement in OHS, gas exchange, daytime sleepiness, and pulmonary arterial pressure. However, bariatric surgery had post-operative negative effects that lasted from one month to a year.[40] Perioperative mortality

is about 0.5% to 1.5%. Intestinal leak occurred in 2–4% of patients, with pulmonary embolism occurring in 1%.[5]

Hence, bariatric surgery should be considered only when the benefits outweigh the risks. Pharmacotherapy in OHS was adjunctive therapy as it was poorly studied; therefore, it could not replace oxygen therapy (PAP). Medroxyprogesterone and acetazolamide were known respiratory stimulants used as pharmacotherapy in OHS. Medroxyprogesterone affects the hypothalamus through the estrogen-dependent progresterone receptor. It could correct daytime hypoxemia and hypercapnia by increasing hypoxic respiratory drive, yet it had no significant effects on hypercapnic respiratory drive. The adverse effects are venous thromboembolism, decreased libido in women, and erectile dysfunction in men. Acetazolamide is believed to be beneficial by inducing metabolic acidosis, which then augments the minute ventilation.[5,6]

The use of both medications should be closely monitored. We already planned to administer the continuous use of PAP as maintenance therapy and also a weight reduction program for our patient following hospital discharge if he could survive. We recognized that the study of aminophylline in OHS was very limited, although it was notable as a respiratory stimulant.[41,42] In a case report, aminophylline was used as a respiratory stimulant to manage OHS.[43]

The management of AHRF in OHS mainly involved oxygen therapy with positive pressure to overcome the hypercapnia. The success rate of NIV in treating AHRF was claimed to be 91% in a retrospective study. The median time to correct the respiratory acidosis was 2.9 days. High success rates were found in OHS subjects with acute decompensation and also with high $PaCO_2$.[15] Nevertheless, a systematic review by Nicolini et al pointed out that NIV failure in OHS patients with AHRF ranged from 2% to 60.5%. NIV failure and mortality were associated with pneumonia and multi-organ failure.[44]

Although there were no RCTs investigating the efficacy of NIV in OHS, it has been listed as standard practice for managing AHRF in this case. Access to NIV should be available for a maximum of an hour from the acute onset of the patient in the emergency department. Administration of NIV should be applied as much as tolerated during the first 24 hours of admission, and once the respiratory acidosis has been corrected and hypercapnia has resolved, weaning of NIV will be performed. The decision to continue home therapy using PAP should be considered based on the presence of ongoing respiratory failure, stability of NIV, and local care pathways.[4]

The NIV is recommended for OHS patients experiencing AHRF. Full-face oronasal masks are generally recommended for less air leakage and higher tidal volume. Both are necessary to enhance alveolar ventilation. In addition, oronasal masks are better tolerated in acute settings because OHS patients with

AHRF tend to breathe using their mouth. Nonetheless, nasal masks are preferred for long-term use as oronasal masks are less efficient and are correlated with poor adherence plus great side effects.[3]

There are no guidelines regarding the use and titration of NIV. However, BaHammam proposed an algorithm for that matter. Treatment inititation is recommended using BiPAP with an Expiratory PAP (EPAP) of 4-6 cm H_2O and an Inspiratory PAP (IPAP) of 8-10 cm H_2O. The EPAP should be escalated gradually until there are improvements in snoring, witnessed apneas, and oxygen saturation, whereas IPAP should be gradually increased to achieve SpO_2>90%. The response to NIV was evaluated by monitoring the vital signs, level of consciousness, respiratory pattern, and arterial blood gases in the first 6 hours. Intubation should be considered if there was deterioration in the monitoring, NIV intolerance, instability of the hemodynamics, agitation, abdominal distention, inability to clear secretions, or if there was upper gastrointestinal bleeding.[13,45]

Endotracheal intubation in OHS patients must be very challenging because of their limited mouth opening and neck mobility. The NIV should be used continuously during the daytime and at night. It could be weaned for night use and 6-8 hours of daytime use whether or not improvements were observed. The weaning could also be performed for night use only once acid-base stability was already achieved (pH>7.35). [13,45] The use of BiPAP in our patient was already appropriate according to the algorithm. It was evidenced by improvements in symptoms, consciousness, vital signs, and ABGA. The other comorbidities for causes of dyspnea were also managed properly.

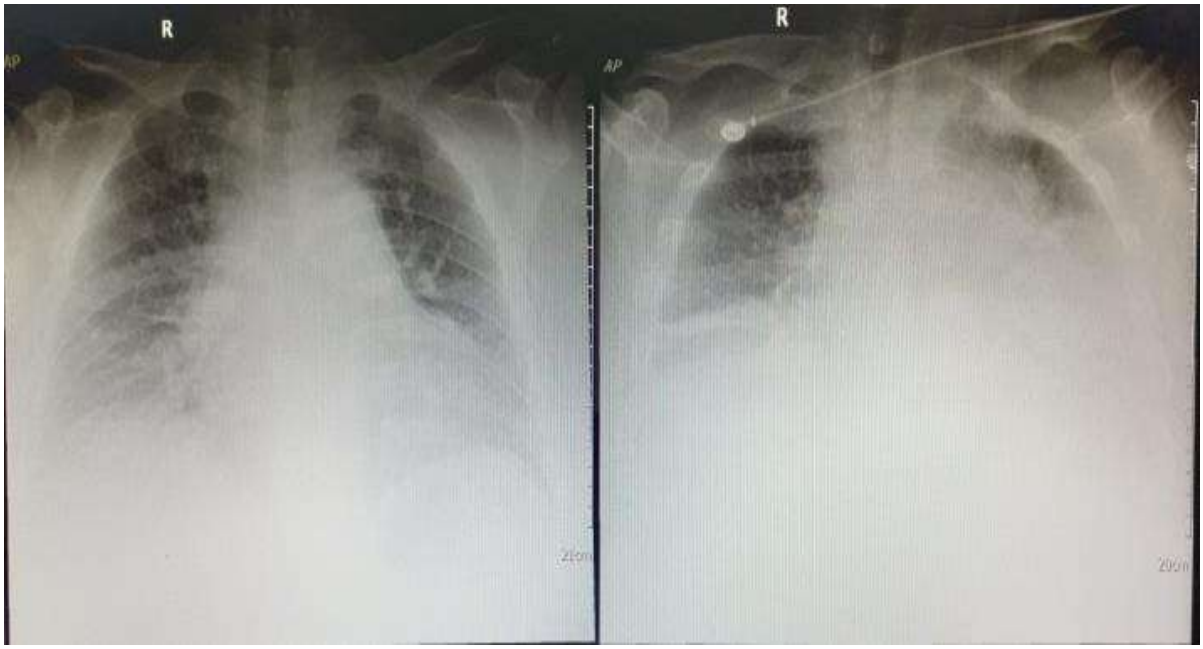

Figure 1. Left. Chest X-Ray: Cardiomegaly with pulmonary vascular congestion and interstitial pulmonary edema; Right. Chest X-Ray 6 days later: Increased lung opacity (worsening)

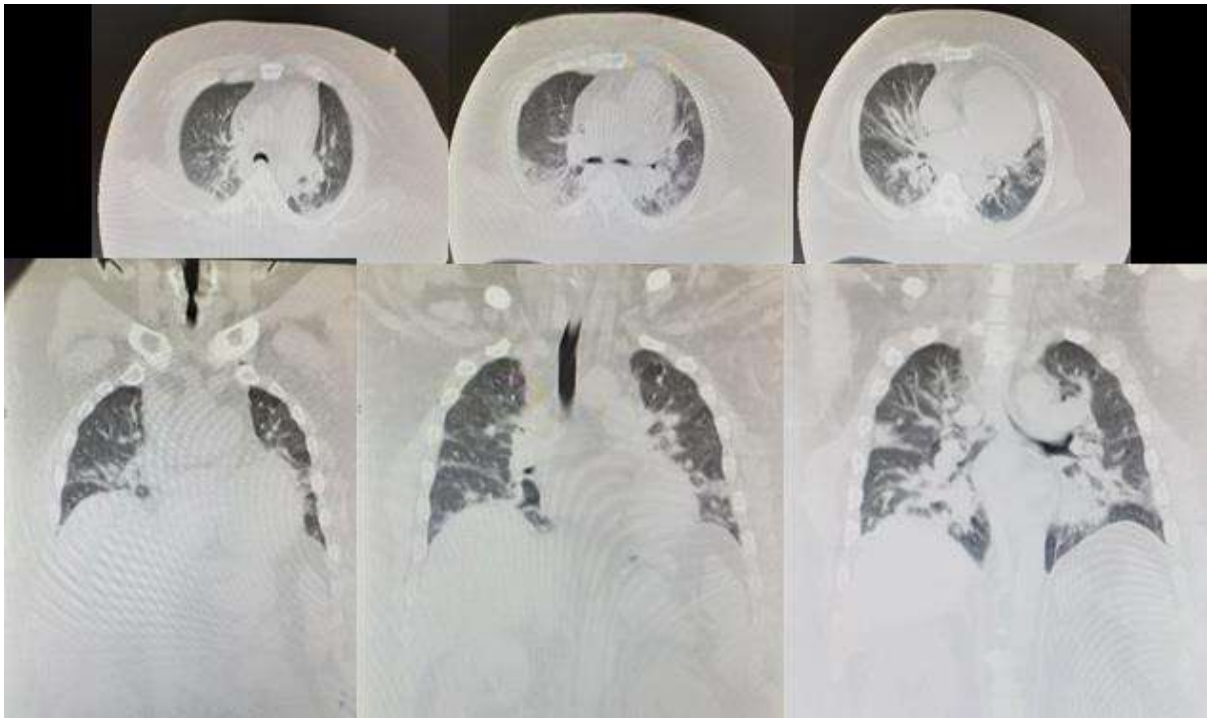

Figure 2. Chest CT-Scan: cardiomegaly with pulmonary vascular congestion, pulmonary edema and pneumonia

CONCLUSION

Based on our findings, there were multiple possible causes of dyspnea in this patient. We believe that this unusual Pickwickian syndrome or so called malignant obesity hypoventilation syndrome which has more comorbidities and/or organ dysfunctions will be found more often in the future, notably in the population with increasing prevalence of obesity. We should also not omit the possibility of COVID-19 as a concurrence in malignant OHS case. Management of patient ought to treat not only the OHS but also all the comorbidities. In consequence, by identifying each of the possible comorbidities (especially those producing dyspnea) and treating them plus the OHS itself, the management will be optimal and should be minimizing mortality in OHS patients.

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Literature Review

Chemotherapy in Lung Cancer with Hepatic and Renal Impairment

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Abstract

Chemotherapy is one of the therapeutic modalities for lung cancer. Chemotherapy with anticancer drugs has a narrow therapeutic index and pharmacokinetic variability between individuals. The administration of anticancer drugs should consider many factors that may affect the pharmacokinetics of the drug, such as hepatic and renal function. In lung cancer patients who have hepatic and renal impairment, an adjusted dose of anticancer drug is needed to achieve levels of drug exposure similar to patients who have normal organ function and avoid toxicity. Renal function is calculated by the glomerular filtration rate or creatinine clearance. Assessment of hepatic function can be taken from Child Pugh's score or from bilirubin and aminotransferase enzyme data in patients. In addition, hepatitis screening is also required. The results of the assessment will determine the adjustment dose recommendation for anticancer drugs.

Keywords: chemotherapy, lung cancer, hepatic impairment, renal impairment

INTRODUCTION

Cancer is a significant disease problem globally and affects 100 million individuals worldwide.[1] Globally, cancer is the leading cause of death. Globocan data states that in 2020 there were 19.3 million new cases with a death rate of 10.0 million deaths.[2,3]The incidence of cancer in Indonesia (136.2/100,000 population) is ranked 8th in Southeast Asia, while in the Asian continent, it is 23rd. The highest incidence of cancer in Indonesia for men is lung cancer which is 19.4/100,000 population (average death rate is 10.9/100,000 population), followed by liver cancer at 12.4/100,000 population (7.6/100,000 population average death). In women, the highest incidence of cancer is breast cancer, 42.1/100,000 population (average death is 17/100,000 population), followed by cervical cancer at 23.4 per 100,000 population with an average death rate of 13.9 per 100,000 population.[3]

Lung cancer is one of the most deadly and common types of cancer globally. Lung cancer is the leading cause of cancer worldwide, accounting for up to 13% of all cancer diagnoses. In 2018, more than 1.7 million people died from lung cancer. Based on the origin of the cells, about 80–85% of lung cancers are non-small cell carcinomas (NSCLC), which are further divided into lung adenocarcinomas, squamous cell carcinomas, and large cell carcinomas based on histology.[4,5]

One of the therapeutic modalities in cancer patients is the administration of chemotherapy or anticancer drugs. However, anticancer drugs have a characteristic narrow therapeutic index and sizeable pharmacokinetic variability between individuals.[1] In general, anticancer drugs are administered at their maximum tolerated dose. Therefore, understanding the effects of pharmacokinetic changes in certain anticancer drugs is essential to determining the appropriate initial amount to maximize efficacy and avoid toxicity.[6]

The administration of anti-cancer drugs must consider other factors that may affect the pharmacokinetics of the drug, such as liver and kidney function[6] as well as excretion of drugs.[1] Renal and hepatic impairment are common disorders in the general population, including cancer patients.[6]

Renal function is an essential consideration in managing patients with advanced cancer. There is a reciprocal relationship between cancer and the kidney. Chronic kidney disease may increase the risk of developing cancer, and patients with cancer often develop renal impairment due to age, disease-related factors, and nephrotoxic treatment.[7] Previous studies have shown that approximately 55% of patients with cancer have an estimated glomerular filtration rate of less than 90 mL/min and about 15% of patients have an estimated glomerular filtration rate of less than 60 mL/min.[6]

For liver disorders, specific prevalence data for patients with cancer has not yet been found. Liver disorders can reduce metabolic capacity, bile outflow, hepatic blood flow, and plasma protein levels, leading to increased exposure to the parent compound. Therefore, understanding drug metabolism pathways and pharmacokinetic changes is critical in making dosing decisions.[6] Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection is associated with significant morbidity and mortality in patients with cancer. According to research, hepatitis B infection is related with a poor outcome in chronic kidney disease (CKD) patients.[8,9]

PHARMACOKINETICS OF ANTICANCER DRUGS

Pharmacokinetics can be defined as the science of absorption, distribution, metabolism, and excretion. In simple terms, pharmacokinetics is defined as what the body does to the drug, which is depicted in Figure 1.[10]

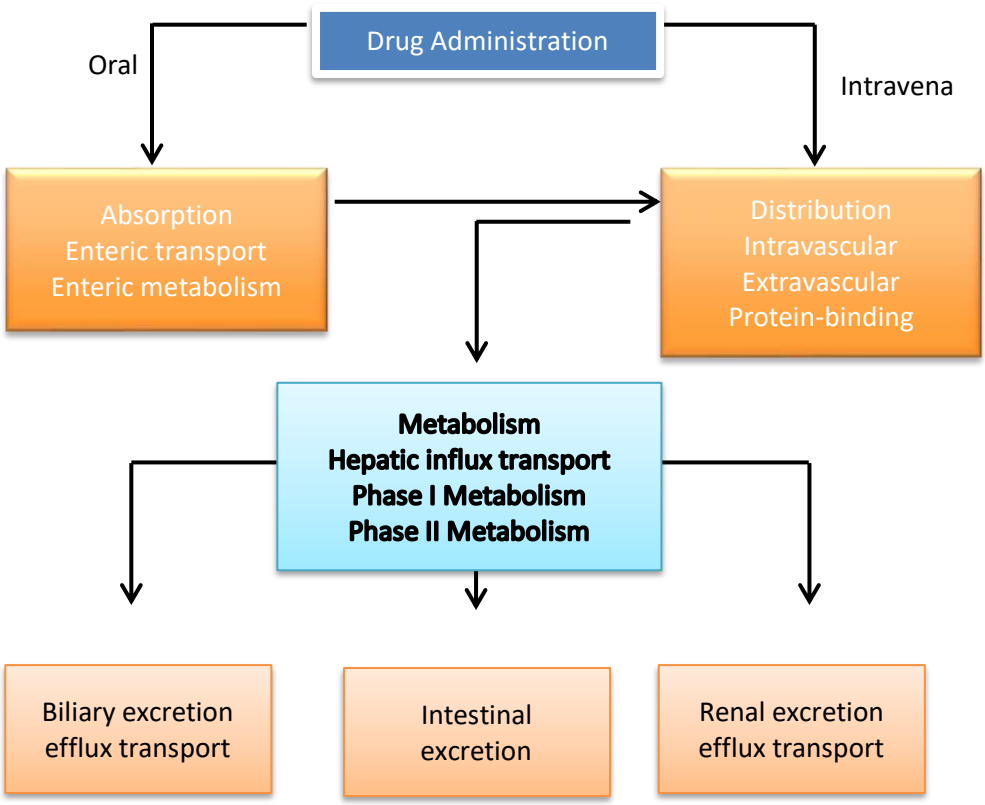

Figure 1. Chart of Drug Pharmacokinetic Processes in General[10]

Drug Absorption

Most anticancer drugs are given intravenously or orally. Intravenous drug administration is the most direct route and results in rapid and complete bioavailability. In contrast, the bioavailability of oral drugs still depends on absorption barriers. As a result, oral medications typically have much greater pharmacokinetic variability than intravenous drugs. Intestinal absorption is regulated by absorption surface area, intestinal transit time, blood flow to the absorption site, and gastric and intestinal pH. It is also influenced by genetic differences in the transport system and drug metabolism in the gut.[10]

There is a drug-efflux pump in the intestinal transport system, namely P-glycoprotein (P-gp) encoded by ABCB1. The presence of polymorphisms in ABCB1 causes variations in P-gp activity, which causes variations in drug pharmacokinetics.[10]

P-gp is expressed in the intestinal epithelium and actively removes drugs from tumor cells, thereby inhibiting the absorption of oral anticancer drugs. Intestinal drug metabolism is affected by CYP3A, a subclass of cytochrome P450 enzymes. The cytochrome P450 enzyme is an intracellular heme-containing oxidizing enzyme responsible for the first phase of the metabolism of many drugs. CYP3A itself is located in the liver and intestines. In the gut, CYP3A4 is the predominant P450 enzyme (70%), located on the crest of mature enterocytes and adjacent to the junction of the intestinal microvilli. CYP3A4 polymorphisms may influence the pharmacokinetic differences of a drug.[10]

Drug Distribution

After absorption or intravenous administration, the drug is distributed from the intravascular space to its target in the extravascular space. Most drugs are bound to plasma proteins such as albumin and glycoprotein acids. The amount of drug moving into the extravascular space depends on how much protein-bound and free drug there is, with only the non-protein-bound or "free" drug being pharmacologically active. Protein binding is usually a saturated process, so differences in plasma protein levels between patients will result in differences in drug distribution.[10]

Drug Metabolism

Metabolism is the most important and complex step in drug disposition and can be a significant source of pharmacokinetic variability. A transporter protein, namely organic anion-transporting polypeptide (OATP), carries drugs and their metabolites from the blood to hepatocytes. Once in the liver, anticancer drugs undergo phase I and phase II reactions.[10]

Phase I reactions change the medicine to be more polar and easily excreted to become inactive, more active, or less active. In contrast, the phase II reaction is conjugation with endogenous substrates such as glucuronic acid, sulfuric acid, acetic acid, or amino acids. Consequently, the drug almost always becomes inactive.[10]

In the most critical phase I metabolic reactions, the primary process is oxidation, catalyzed by the enzyme cytochrome P-450 (CYP450) monooxygenase in the endoplasmic reticulum (microsome) of the liver. The majority(50%) of medicines are metabolized by CYP3A4, a cytochrome P450 enzyme located largely in the liver and intestines. Therefore, the CYP3A4 enzyme plays a critical role in the metabolism and first-pass elimination of various drugs.[10]

Phase II reactions conjugate phase I products to form derivatives that are usually inactive for renal and biliary elimination. The most critical process is glucuronidation via the enzyme UDP-glucuronyl-transferase (UGT), which mainly occurs in liver microsomes and extrahepatic tissues (small intestine, kidney, lung, skin). Other conjugation reactions (acetylation, sulfation, conjugation with glutathione) occur in the cytosol.[10]

Drug Excretion

The main routes of drug excretion are through the bile ducts and kidneys. Mechanical obstruction of the biliary tract due to hepatic metastases may impair biliary excretion, and decreased serum albumin associated with malnutrition has been associated with decreased biliary excretion of anticancer drugs. Some anticancer drugs, such as platinum compounds, are eliminated mainly through the kidneys. The presence of renal insufficiency characterized by a decrease in the glomerular filtration rate (GFR) can reduce drug clearance. GFR can decrease with age.[10]

ACTION MECHANISM OF ANTI-CANCER DRUGS

The stages of the cell cycle are divided into two main phases (interphase and mitosis). In the interphase, cell growth and DNA copying occur. This phase begins with the G1, where the cell grows enlarged, organelles are copied, and molecular walls are formed. The S phase is when the cell synthesizes a copy of DNA in its nucleus. Cells also duplicate microtubule-organizing structures called centrosomes. Centrosomes help separate DNA during the later M phase. The G2 phase is characterized by an increasing number of cells. They also form proteins and organelles in this phase. Once all is well, the mitosis phase is ready to begin. The mitosis phase of the cell divides the DNA and cytoplasm that have previously been copied into two parts and the cell itself divides. In this mitosis phase, there are four stages that occur. The stage begins with prophase, metaphase, anaphase, and ends with telophase.[11]

Anti-cancer drugs interact with DNA in various ways. The formation of complexes between DNA and drugs will lead to changes in the thermodynamic stability and functional properties of DNA.[11] Pharmacodynamics of anti-cancer medications depends on how the drug itself works. Some anti-cancer drugs act in non-spesific phases. And some drugs act on certain specific phases of the cell cycle. For example, antimetabolites are mainly active during the G1 and S phases, and topoisomerase inhibitors target the S phase, whereas spindle toxins are only involved in mitotic cells. As shown in Figure 2, there are four classes of anti-cancer drugs commonly used for the treatment of lung cancer, which are as follows:[12]

1. Alkylation drugs, including cisplatin and carboplatin, directly damage DNA by interrupting replication and transcription.
2. Antimetabolites (pemetrexed, gemcitabine) interrupt nucleic acid synthesis.
3. Topoisomerase inhibitors are critical enzymes that loosen DNA supercoiling during replication and transcription, including topoisomerase I (topotecan) and topoisomerase II (etoposide).
4. Spindle toxins that interfere with the polymerization or depolymerization of mitotic spindle microtubules, including vinorelbine, paclitaxel, and docetaxel.

Chemotherapy can be used as a neoadjuvant or postoperative adjuvant in early-stage lung cancer. Adjuvant therapy can be given to NSCLC stages IIA, IIB, and IIIA. If the patient's overall appearance is favorable (Karnofsky >60%; WHO0-2), chemotherapy can be given in the advanced stage of NSCLC. However, the most significant benefit of chemotherapy is as palliative therapy in patients with advanced stages.[5]

The first line is given to patients who have never received chemotherapy treatment for lung cancer. This group consists of platinum-based and non-platinum-based chemotherapy (new generation drugs).

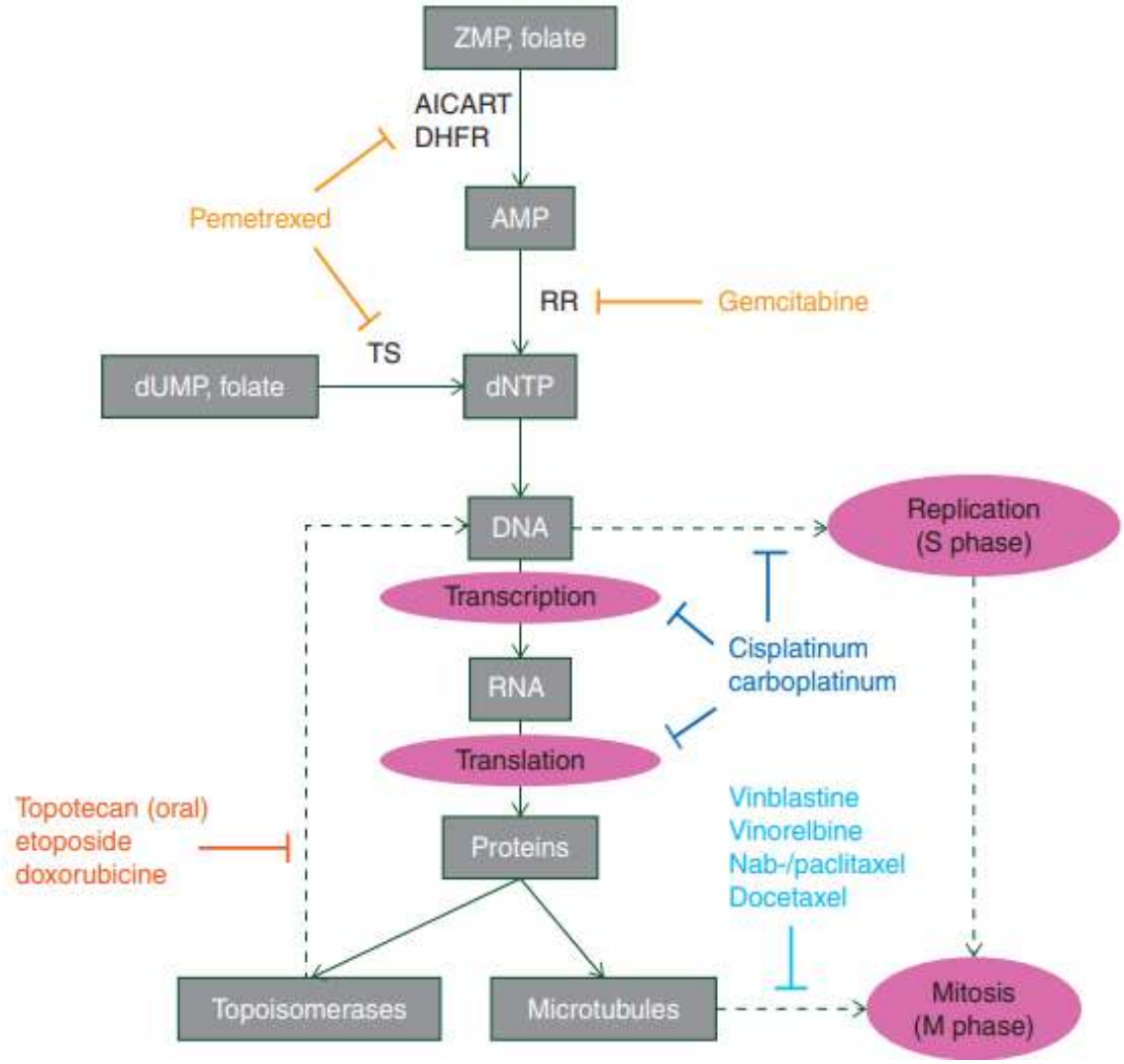

Figure 2. Mechanism of Action of Anti-cancer Drugs on Lung Cancer[12]

The primary choice for platinum-based medicines is cisplatin, with carboplatin as the other option. The non-platinum-based first-line chemotherapy drugs that can be given are etoposide, gemcitabine, paclitaxel, and vinorelbine. The combination of cisplatin with gemcitabine provides the highest survival rate, but the best response is to the cisplatin regimen with paclitaxel.

Second-line chemotherapy was given to patients who received first-line chemotherapy but did not respond after 2 cycles or became more progressive after chemotherapy was completed. Second-line chemotherapy drugs are docetaxel and pemetrexed. In addition, a combination of two non-platinum-based drugs may also be given. Third-line chemotherapy and beyond is highly dependent on the history of previous treatment.[5,13]

KIDNEY DISORDER ASSESSMENT

Renal function is usually expressed as an estimate of the glomerular filtration rate based on creatinine clearance. Measuring the glomerular filtration rate with the

isotopic marker Cr-EDTA is considered the gold standard in patients with cancer. However, this approach is not routinely used in practice because of its high cost.[6] Different methods for measuring glomerular filtration rate, e.g., 24-hour urine test or calculations using the Martin, Wright formula, Cockcroft and Gault formula, MDRD, or Chronic Kidney Disease formula Epidemiology Collaboration [CKD-EPI]).[7] Currently, the recommended guideline is the use of the CKD-EPI formula for estimating the glomerular filtration rate.[6,8] The differences between several methods of measuring glomerular filtration rate can be seen in Table 1.[14]

After estimation of renal function is performed, Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) have defined the stratification of the degree of kidney disorders as in Table 2. This international definition should also be used in patients with cancer.[15–17]

Renal impairment may affect 1 or more of the 4 pharmacokinetic phases (absorption, distribution, metabolism, and elimination/excretion). Reduced renal function can reduce the excretion of metabolites from anticancer drugs because anticancer drugs are eliminated either wholly or partially in the kidney. This decreased excretion can lead to drug accumulation and increased exposure to toxicity.[6] This disorder can cause modifications in the pharmacokinetic profile of the drug administered so that an adjustment in the dose of anticancer drugs is required to avoid drug accumulation and reduce side effects.[6,15]

Table 1. Several Methods of Measuring Glomerular Filtration Rate

Formula	Formulation
Creatinin clearance	
Cockcroft-Gault, ml/minute	(140-age) x BB x (1-0.15x sex) / Cr x 0.814
Jelliffe, ml/minute	(98-0.8x(Age-20)) x (1-0.1x sex) x BSA/1.73)/Cr x 0.0113
Wright, ml/minute	(6580-38.8x age) xBSAx (1-0.168x sex)/Cr
Calculation of eGFR	
Modification of Diet in Renal Disease (MDRD)	GFR = 186 x SCr-1.154x Age-0.203 x 1.212 (if the patient is black) x 0.742 (if female)
CKD-EPI creatinine	SCr 0.7 (female) and SCr 0.9 (male) 144x(SCr/0.7)-0.329x0.993age x (1.159 if black race) (if female) 141x(SCr/0.7)-0.411x0.993age x (1.159 if black race) (if male) SCr 0.7 (female) and SCr 0.9 (male) 144x(SCr/0.7)-1.209x0.993age x (1.159 if black race) (if female) 141x(SCr/0.7)-1.209x0.993age x (1.159 if black race) (if male)
CKD-EPI Cystatin C	For all Scys grades 0.8 or 0.8 133 x (Scys/0.08)-0.499x0.996age x 0.932 (if female) 133 x (Scys/0.08)-0.499x0.996age x 1.0 (if male)
Cancer-specificGFR equations	
Calvert formula	Dosage (mg) = AUC x (GFR +25)
Martin formula	163 x ABW (1-0.00496 x age) x(1-0.252xsex)

Note: BB=body weight; Cr=creatinine; BSA=body surface area; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; SCr=serum creatinine; SCys=serum cystatin; AUC=area under the curve; ABW=actual body weight

Table 2. Stratification of the degree of renal impairment based on KDOQI and KDIGO[16]

Stadium	Description	GFR
Patients with an increased risk	Risk factors for kidney disease (such as diabetes, hypertension, family history, old age, etc.)	Over 90
1	Renal impairment and normal GFR	Over 90
2	Renal impairment and mild decrease in GFR	60 – 89
3	Moderate decline in GFR	30 -- 59
4	The GFR weight loss	15 – 29
5	Kidney failure (dialysis or need a kidney transplant)	<15

Note: Signs of kidney disorders: proteinuria, hematuria, etc. GFR: glomerular filtration rate

In patients with renal impairment, the dose reduction is expected to be directly proportional to the percentage decrease in the glomerular filtration rate. For the most part, anticancer drugs undergo biotransformation in the liver, where more and more water-soluble metabolites can be excreted via the kidney, where the required dose adjustment is more complex to predict. Anticancer drugs with a more comprehensive therapeutic index or large inter-individual variability may not directly require dose adjustment. Patients should also receive adequate hydration and careful monitoring of decreased renal function.[6,7]

There are three methods to adjust the dose according to the degree of renal function:[18]

1. Reducing the unit dose without modifying the dosing interval
2. Increasing the dosing interval without lowering the unit dose
3. Reducing the unit dose and increasing the dosing interval

In patients with renal impairment undergoing hemodialysis, information about the effect of hemodialysis on the pharmacokinetics of anticancer drugs is usually only found in case reports or small case series. Drug clearance in patients undergoing hemodialysis is determined by drug characteristics (e.g., protein-bound fraction, molecular weight, and volume of distribution), dialysis characteristics (e.g., pore size and flow rate), and patient characteristics (e.g., albumin level and residual renal function). For anticancer drugs that are excreted via the kidneys, dose adjustment is often necessary for patients undergoing hemodialysis.[19]

LIVER DISORDER ASSESSMENT

Liver metabolism plays a very important part in the pharmacokinetics of many chemotherapeutic drugs, especially their activation, degradation, and excretion.[9] For liver function, the FDA and EMA recommend using the Child-Pugh scoring system to assess the effects of hepatic impairment. The Child-Pugh score consists of bilirubin, albumin, and prothrombin levels along with the presence or absence of encephalopathy and ascites, as shown in Table 3.

Initially, the Child-Pugh score was only developed to predict operative mortality in patients with liver cirrhosis. However, the Child-Pugh score is often used as a scale to assess liver disorders.[6,20]

Table 3. Assessment of *Child Pugh* scores based on clinical and laboratory criteria[6]

	1 point	**2 points**	**3 points**
Total bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3-5	2.8-3.5	<2.8
Prothrombin time (second lengthening) or INR	<4 or <1.7	4-6 or 1.7-2.3	>6 or >2.3
Ascites	None	Mild	Medium
Encephalopathy (grade)	0	1 or 2	3 or 4

Note: INR=international normalized ratio. Grade A (with) = 5-6 points, Grade B (moderate) = 7-9 points, Grade C (heavy) = 10-15 points.
Encephalopathy; Grade 0 = normal consciousness, behavior, neurologic examination, and EEG. Grade 1 = sleep disturbances, restlessness/irritability, tremors, writing disorders. Grade 2 = lethargy, time disorientation, mismatch, asterixis, ataxia. Grade 3 = somnolence, stupor, site disorientation, reflex hyperactivity. Grade 4 = comma.

The FDA and EMA guidelines note the importance of verifying that those changes in the Child-Pugh component result from liver disease and are not caused by other underlying diseases such as cancer. *The National Cancer Institute Organ Dysfunction Working Group* recommends rating liver dysfunction as mild, moderate, or severe based on total bilirubin and transaminase concentrations, with bilirubin contributing most to metabolic capacity.[6,20]

The liver is the main organ for drug metabolism and excretion for most anti-cancer drugs. The liver is the main organ that functions for drug metabolism and excretion, most of which are anti-cancer drugs. Liver function impairment is most common in patients with cancer, i.e., disorders caused by liver metastases. However, it could also be due to other factors such as hepatotoxicity from previous cancer treatments, cirrhosis, or hepatitis.

The impact of liver dysfunction on drug disposition is related to the type and severity of hepatic impairment as well as the physicochemical and pharmacokinetic characteristics of the drug.[20] Biotransformation of drugs in the liver is very important for detoxifying active compounds and toxic metabolites and activating prodrugs. Therefore, reduced metabolic capacity can have profound effects on anticancer drug exposure.[6] The less active metabolites are formed, the less effective therapy is in the patient. Reduced metabolic capacity may occur as a direct result of functional hepatocyte loss or an indirect result of the altered activity of drug-metabolizing and drug-transporting enzymes.[9,20]

Inhibited cytochrome P450 CYP3A4 activity has been reported in patients with cancer with an acute-phase inflammatory response. However, currently, liver serum biochemical tests do not provide an adequate assessment of the liver's metabolic capacity.[21]

Apart from the consequences of altered metabolic capacity, liver metastases and causes other than malignancy may also interfere with liver biochemical tests. In addition to decreased metabolic capacity, some changes in bile excretion, hepatic blood flow, and plasma protein binding may also occur in patients with hepatic impairment. Obstruction of biliary excretion can lead to drug accumulation, leading to hepatocellular damage.[6]

Before starting treatment, HBsAg and anti-hepatitis B screening should be performed in patients at high risk for HBV infection (i.e., patients from areas of high HBV endemicity, with a history of intravenous drug abuse, on hemodialysis, or who are HIV-positive, or homosexual men). Hepatitis B reactivation, defined as the development of hepatitis with elevated serum HBV DNA levels, is a complication in cancer patients undergoing cytotoxic chemotherapy and can lead to death. This risk was related to the status of HBV infection before chemotherapy and the degree of immunosuppression during chemotherapy. Antivirals are given 1-2 weeks before chemotherapy and are maintained until the immune condition improves, although it is difficult to define.[22] In cases of high risk of reactivation, prophylactic lamivudine significantly reduces the prevalence of HBV reactivation in patients with hematological malignancies and patients with solid tumors.[8,9,23]

HCV infection is more common than HBV infection in cancer patients. Therefore, if an anti-HCV screening is positive, a qualitative HCV RNA PCR examination will be continued.[23] Patients with positive anti-HCV will then be tested for HCV RNA PCR. In addition, it is necessary to carefully monitor HCV viral load and alanine transaminase (ALT) levels during and after chemotherapy.8 There is no established prophylaxis for HCV infection. However, in chronic hepatitis C, alpha interferon and ribavirin can be given, which is said to be effective.[8,9]

CHEMOTHERAPY DOSAGE ADJUSTMENT IN LIVER AND KIDNEY DISORDERS

Based on the liver and kidney function data, it is possible to recommend the dose to be given, namely the full dose recommendation, percent recommendation, the specific recommendation in milligrams per square meter, or recommendation to postpone administration. Adjustment of the dose of anti-cancer drugs for chemotherapy in lung cancer can be seen in Table 4.[8]

In lung cancer, anti-cancer drugs that require dose adjustment in renal impairment are cisplatin, carboplatin, etoposide, and pemetrexed. Cisplatin is not recommended in renal impairment with a GFR <60. Pemetrexed is also not recommended if the GFR is <45.

At the same time, drugs that require dose adjustment in liver disorders are paclitaxel, gemcitabine, etoposide, and vinorelbine. Docetaxel is only given when there is no liver disorder. Etoposide is not recommended if the bilirubin is more than 2.5 times normal. Paclitaxel is also not recommended if the bilirubin is more than 3.5 times normal.

Cisplatin is a platinum-based chemotherapy that is often used as a single drug or in combination to treat solid tumors, including lung cancer. However, the use of cisplatin is limited by its side effect profile, particularly dose-dependent nephrotoxicity. The kidneys excrete cisplatin by glomerular filtration and tubular secretion.[24]

Table 4. Adjustment of doses of anti-cancer drugs given to lung cancer with liver and kidney disorders[8]

Medicine Name	Kidney Disorders	Liver Disorder
Cisplatin	1. GFR >60, dose 75 mg/m2 every 3 weeks 2. GFR < 60, not recommended	---
Carboplatin	3. GFR > 60, AUC5 or AUC6 doses every 3 weeks	---
Pemetrexed	1. GFR <60, as per Calvert or Chatelut formula 2. GFR 45 - >60, dose 500 mg/m2 every 3 weeks 3. GFR < 45, not recommended	---
Etoposide	1. GFR >60, dose 100-120 mg/m2 every 3 weeks 2. GFR 15-60, dose 75 mg/m2 every 3 weeks 3. GFR <15 or hemodialysis, dose 50 mg/m2 every 3 weeks	1. Normal, dose 100-120 mg/m2 on H1,2,3 every 3 weeks 2. Bilirubin > 1.25-2.5x N, dose reduced by 50% 3. Bilirubin >2.5x N, not recommended
Gemsitabin	---	1. Normal, dose 1000-1250 mg/m2 2. AST-ALT-Bilirubin >1-3x N, dose 800 mg/m2
Paclitaxel	---	1. Normal, dose 175-200 mg/m2 every 3 weeks 2. AST-ALT>N, dose 135 mg/m2 every 3 weeks 3. Bilirubin >1.25-2x N, dose 115 mg/m2 every 3 weeks 4. Bilirubin >2-3.5x N, dose 100 mg/m2 every 3 weeks 5. Bilirubin >3.5x N, not recommended
Dosetaxel	---	1. Normal, 75 mg/m2 every 3 weeks 2. Num > N, not recommended 3. AST-ALT >1.5x N, not recommended
Vinorelbine	---	1. Normal, dose 25-30 mg/m2 per week 2. Bilirubin >1.75-2.5x N, dose reduced by 50% 3. Bilirubin >2.5x N, dose reduced by 75%

Note: GFR=glomerular filtration rate; AUC=area under curve; num=bilirubin; AST=aspartate aminotransferase; ALT=alanine aminotransferase

If there has been a decline in renal function before cisplatin administration, it is recommended to use another platinum-based chemotherapy drug with less nephrotoxic effect, such as carboplatin. Renal function should be observed one week after cisplatin administration.[25]

Most damage occurs in the proximal tubule. This is also because cells in the proximal tubule take up cisplatin via organic cationic transporter-2 (OCT-2). The accumulation of cisplatin in the proximal tubule results in cellular damage due to oxidative stress and the production of pro-inflammatory cytokines. TNF-, a potent inflammatory mediator, causes apoptosis. Cisplatin also activates p53 and signaling pathways, such as mitogen-activated protein kinase, which promote cell death.[26]

Carboplatin has a lower nephrotoxic effect than cisplatin due to the lack of chloride ion content and lowers drug uptake via OCT-2.[26] Therefore, carboplatin is said to have good pharmacokinetic and pharmacodynamic effects in CKD patients. However, most carboplatin will bind to protein after 24 hours, so hemodialysis is carried out after 24 hours.[19]

Pemetrexed is a methotrexate derivative and an antifolate drug that inhibits enzymes involved in purine and pyrimidine metabolism by inhibiting DNA and RNA synthesis. Pemetrexed can be used as a single drug or combined with other antineoplastic drugs such as cisplatin

or carboplatin. Pemetrexed is excreted through the kidneys in an unchanged form. According to the FDA, for information on how to use pemetrexed, no dose adjustment is required in patients whose CrCl is above 45 mL/min/1.73m^2. Below this limit, administration of pemetrexed is not recommended because there is an increased risk of toxic effects. Pemetrexed can cause damage to the renal tubules, resulting in ATN.[27]

The risk of nephrotoxicity is higher in patients who who have previous nephrotoxic chemotherapy and in patients who have risk factors for CKD, such as diabetes and hypertension. In addition, apical folate receptors and basolateral folate carriers can carry pemetrexed to the renal tubules, causing nephrotoxicity.[26] Patients with AKI may experience improvement in renal function after discontinuation of pemetrexed, although the renal function does not improve in some patients, and interstitial fibrosis develops.[27]

CONCLUSION

Chemotherapy with anticancer drugs is given at the maximum tolerated dose and is calculated based on the body surface area. The characteristics of anticancer drugs that have a narrow therapeutic index and large pharmacokinetic variability between individuals require special attention. Understanding the effects of pharmacokinetic changes in certain anticancer drugs is very important to determining the appropriate dose to achieve maximum efficacy and avoid toxicity. Administration of anticancer drugs must consider other factors that may affect drug pharmacokinetics, such as renal and hepatic function. Most anticancer drugs are used in combinations that are safe and effective. The goal of adjusting the dose of a particular drug for a patient who may have organ failure is to achieve a level of drug exposure similar to that of a patient with normal organ function. Therefore, benefit and risk assessments should be carried out for each patient individually.

Before giving chemotherapy, an assessment of kidney and liver function was carried out. Renal function assessment calculates the glomerular filtration rate or creatinine clearance. Assessment of liver function can be done from the Child-Pugh score or baseline bilirubin and aminotransferase enzymes in the patient. In addition, hepatitis screening was also carried out. The assessment results will determine the recommended dose of anti-cancer drugs given to achieve treatment goals.

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Literature Review

Air Pollution and Respiratory Diseases During The Hajj Season in The Holy City of Makkah

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Abstract

The holy city of Makkah is one of the big cities in Saudi Arabia that is densely populated, especially during the Hajj season. In recent years, air pollution in Makkah has been a growing problem due to construction activities, motor vehicle fumes, rising temperatures, rainfall and humidity. The higher the level of air pollution exposure, the more it has an impact on human health, especially the lungs and airways. The health impacts associated with air pollution include an increase in the incidence of respiratory infections, asthma, chronic obstructive pulmonary disease and other lung diseases. Better knowledge of the correlation between air pollution and lung and airway diseases will contribute to developing more strategies to reduce air pollution in the holy city of Makkah.

Keywords: air pollution, pilgrims, holy city of Makkah, respiratory disease

INTRODUCTION

Hajj is the fifth pillar of Islam. Around three million Muslims worldwide travel to the holy city of Makkah and perform various prayers in Makkah, Arafah, Muzdalifah, and Mina. During the pilgrimage season in the area, the human population increases significantly, and the activity is very high. Pilgrims spend several days on foot, driving cars, buses, trucks, and trains from one place to another, so these various activities produce a lot of air pollutants. In Makkah, the air quality data shows that air pollution during the Hajj season is among the worst in the world. This literature review will discuss the condition of air pollution and respiratory diseases in the holy city of Makkah during the Hajj season.

AIR POLLUTANTS IN THE HOLY CITY OF MAKKAH

Particle

In terms of health impacts, environmental damage, and impaired visibility, particulate matter (PM) is considered one of the most important air pollutants. Particle size, chemical composition, and pollution levels in the

atmosphere are essential factors affecting human health. The size of the particles defines where they are deposited in the respiratory tract, while the chemical composition of the particles determines the sort of body response.

Habeebullah et al. conducted research in the Shebeka, Aziziah, Masfalah, and Awaly districts of Makkah. When compared to the proportion of total suspended particles (TSP), medium and coarse PM sizes are the most prevalent.[1]

Habeebullah conducted the investigation to assess the levels and chemical composition of TSP, PM10, and PM2.5. Total suspended particles, PM10, and PM2.5 were detected in Makkah from August 2012 to September 2013. Heavy metals, cations, and anions were also analyzed. The study revealed that a significant majority of PM is not caused by fossil fuels, but rather by particle re-suspension, building, and demolition operations, as well as dust and sand particles driven by the wind. Research is needed to discover the specific source of PM in Makkah as part of efforts to enhance air quality in the city.[2]

Mohammed conducted a study to measure the spatial variation of PM10 in Makkah. In the north-western part of Makkah, PM10 levels are higher than in the southeast. The intensity of construction activities, transportation on highways, and city development in various locations in the central area of Makkah is the biggest contributor to the high levels of PM10.[3]

In the 2013 Hajj season, Khwaja et al. conducted a study to assess the air quality around the holy place of Makkah. They measured PM7, PM2.5, O3, and black carbon (BC) levels up to 9,433 µg/m3, 484 µg/m3, 444 ppb, and 468 µg/m3, respectively. This average level has exceeded the standards of the World Health Organization (WHO) for PM10 and PM2.5. High traffic volume, construction activities, particle re-suspension, and geographical conditions (dry areas) are the main causes of air pollution.[4]

In the month of Ramadan and the Hajj seasons of 1424 and 1425 H, Seroji researched the levels of TSP, PM10, and PM2.5 in the air of Makkah and the Mina valley. The daily cycle of PM10 in the air is related to traffic activity patterns. During the pilgrims' presence in Mina, daily levels in the Mina valley air ranged from 191–262µg/m^3 exceeding the European standard of 50µg/m_3. Pollutants contain up to 34%–40% TSP. During the last ten days of Ramadan, TSP levels in Makkah reached 665µg/m^3 compared to the Saudi Arabian standard of 340µg/m^3. Chemical analysis of PM10 shows high levels of sulphate, ammonium, nitrate, and chloride.[5]

PM10 levels and their chemical composition were measured in six locations (Al-Haram, Arafah, Muzdalifah, Aziziyah, Al-Nuzhah, and Al-Awali) in a study conducted by Adly et al. They found that PM10 levels were highly correlated with levels of cadmium, chromium, arsenic, beryllium, and nickel.[6]

Siddique studied air pollution levels in Makkah during the Hajj seasons of 2012 and 2013. Pollutant levels on most pilgrims' travel routes have surpassed WHO

standards for PM10 and PM2.5. High traffic volumes, construction activity, particle re-suspension, and geographical circumstances all contributed to high levels of air pollution (dry areas).[7]

Hazardous Gases

Al-Jeelani conducted a study in Makkah during the Hajj season on January 14-25, 2005, to assess air quality due to emissions from the daily activities of pilgrims associated with increased transportation needs. Measurements of the levels of several harmful air pollutant gases and several meteorological parameters, including temperature, wind speed, and wind direction, were carried out. At the beginning of the day, residents' activities were traveling to work, and high traffic volume had affected pollutants. Carbon monoxide, NO, and NO_2 levels change throughout the day, whereas sulfur dioxide levels remain relatively constant.[8]

Habeebullah conducted a graphical approach to measure the main air pollutant sources near the Al-Haram Mosque in Makkah. Air pollutants considered in this study are nitrogen oxides (NOx), nitrogen dioxide (NO_2), nitric oxide (NO), carbon monoxide (CO), sulphur dioxide (SO_2), ozone (O_3) and particulate matter with an aerodynamic diameter of 10 um or less (PM10). Polar plots, time variation plots and correlation analysis are used to analyse the data and identify the major sources of emissions. Most of the pollutants demonstrate high concentrations during the morning traffic peak hours, suggesting road traffic as the main source of emissions. The density of road traffic, re-suspension of particles, and dust or sand particles blown by the wind are the main sources of pollutant emissions identified in Makkah.[9]

Simpson et al. conducted a research to investigate air pollution levels in Makkah during the Hajj season in 2012. The study discovered significant amounts of carbon monoxide (CO) and volatile organic compounds (VOC) throughout the pilgrimage routes, particularly in the Makkah tunnels. Benzene i-pentane is the most prevalent volatile organic compound. The primary sources of volatile organic compounds are automobile exhaust emissions, gasoline evaporation, liquefied petroleum gas, and air conditioning.[10]

Al-Jeelani conducted a study to measure the impact of motor vehicle emissions on air quality around the Al-Haram Mosque in Makkah. Experimental, numerical, and statistical research were conducted. Several levels of harmful gases due to motor vehicle emissions are measured and analyzed. Research shows that the Masjid Al-Haram area has high levels of harmful gas pollutants. In addition, there was resistance to wind currents due to the height of the buildings around the Al-Haram Mosque.[11]

Research in the Taneem area by Al-Jeelani showed that levels of nitrogen oxides and carbon monoxide in the morning increased, while sulphur dioxide levels were relatively low and constant. In addition, photochemical reactions affect ozone levels.[12]

Microbes

Abdel Hameed conducted a study to measure levels of microbial air pollutants. Using the gravity method, microbial contamination in the air is collected from the main direction of the Al-Haram Mosque in Makkah. In all directions, the concentrations of bacteria, fungi and actinomycetes ranged from 1,470 - 21,800 CFU/m^3, respectively; 44 - 572 CFU/m_3 and 0.0264 CFU/m_3. Bacterial levels differed significantly, and gram-positive bacteria constituted 90-100% of the total bacterial isolates. Gamma proteobacteria are the common gram-negative bacteria, and Aspergillus is the predominant genus of fungi. Human activities have a greater influence on microbial levels than meteorological factors.[13]

Mohammed et al. conducted a study to measure particulate matter and biological contaminants in Makkah during the Hajj season of 1437H. Microbial air samples were collected at five locations around the Al-Haram Mosque. The results showed that the percentage of gram-positive bacteria ranged from 85-90% of the total bacteria isolated, while the percentage of gram-negative bacteria ranged from 5-9% of the total bacteria isolated. Spherical bacteria (cocci) were most commonly found in the gram-positive group and made up 35-80% of the total bacteria isolated. Around the Al-Haram Mosque in Makkah, humans are the main source of microbial air pollution.[14]

Air Allergens

The problem of allergic diseases has increased significantly over the last 50 years. Despite increasingly clear information on pathogenesis, risk factors, and treatment, allergies are on the rise. Allergens are proteins or glycoproteins that can induce a sIgE response. The top five inhalant allergens in the holy city of Makkah are the American cockroach, *Dermatophagoides pteronyssinus,* epithelia/cat hair, dessert palm pollen, and *Dermatophagoides farina*.[15]

AIR POLLUTION AND RESPIRATORY DISEASES

The respiratory tract is the primary portal of entry for air pollutants; consequently the respiratory effects of pollutants have been studied for decades. Table 1 provides examples of common respiratory conditions and outcomes that have been associated with air pollution exposure. Meanwhile, Table 2 provides examples of biomarkers of respiratory health or function that have been used in studies of the respiratory effects of air pollution.[16]

Examples of respiratory clinical effects associated with air pollution:[16]

1. Increased mortality of the respiratory disease
2. Increased incidence of respiratory tract malignancies
3. Increased incidence, prevalence, or frequency of exacerbations in the disease
4. chronic lung: asthma, COPD, and cystic fibrosis

5. Increased incidence or severity of upper respiratory tract infections and
6. lower
7. Increased respiratory symptoms that affect the quality of life:
8. cough, phlegm, wheezing, shortness of breath, and runny nose
9. Increased incidence of preterm birth, low birth weight or growth inhibition
10. Impaired lung function growth in children
11. A temporary decrease in lung function
12. A transient decrease in lung function without symptoms, especially in
13. individuals who are susceptible (e.g., children with severe asthma)
14. The persistent or chronic decline in lung function (weeks, months, or years)

Examples of biomarkers of potentially adverse respiratory health effects:[16]

1. Elevated levels of airway inflammatory markers (e.g., PMN or cytokines in bronchial lavage or phlegm
2. Elevated levels of markers of airway inflammation or inflammation in:
    a. The exhaled breath (e.g., increased acidity)
    b. The exhaled breath condensate or increased FeNO in asthmatics)
3. Elevated blood markers in lung injury (e.g., 8-isoprostane, club cell
4. secretory protein)
5. Imaging evidence of lung injury or reduced lung volume
6. Decreased pulmonary gas exchange (e.g., DLCO, DLNO, PaO2, pulse
7. oximetry)
8. Improved airway responsiveness to nonspecific challenges
9. Increased airway hyper-reactivity in asthmatic patients

There are six types of substances present in the air that have a significant negative impact on public health: ozone, PM with different diameters - PM2.5μ, PM2.5–10 μ, PM10 μ, nitrogen dioxide, sulphur dioxide, carbon dioxide monoxide, and lead. Particular attention should be paid to small dust particles (PM10 and PM2.5) as they can penetrate the lower respiratory tract. The development and worsening of respiratory symptoms such as asthma, chronic obstructive pulmonary disease, respiratory infections, and lung cancer are all caused by air pollution.[17]

Research shows a relationship between air pollution and hospital admissions in adults due to Chronic Obstructive Pulmonary Disease (COPD). Increases in daily NO_2 and particulate matter levels were associated with a 4.60% and 3.01% increase in COPD hospital admission rates, respectively, in Sydney.[18] Another study on hospital admissions in Birmingham, England, reported an association between PM10 and rates of hospital admission due to pneumonia and mortality from COPD.[19]

Mohammed conducted a study in Makkah to evaluate the effect of a crushed mountain environment resulting in the dust on asthma patients. In the group exposed to a dusty environment, asthma symptoms worsened, lung function decreased, and the need for medication for relief and control of asthma attacks increased.[20]

Many previous studies have shown that respiratory infections increase during

the Hajj season. Although upper respiratory tract diseases are prevalent, lower respiratory tract infections (pneumonia) can occur, and the latter is much more deadly than the former. The leading causes of illness include the influenza virus and other viruses and bacteria. The increase in respiratory infections during the Hajj season has severe implications for public health. It can lead to epidemics and adversely affect the economy due to increased health care costs, the need for hospital beds, and lost working days.

Strong evidence suggests an association between air pollution and the severity of illness associated with respiratory tract infections. Individuals with pre-existing lung disease are at higher risk. The majority of pilgrims are adults and the elderly. Complications, hospitalizations, and deaths from respiratory tract infections are most significant in the elderly and those with comorbidities. The disease that most often occurs during the Hajj season is a respiratory infection. The most common causes of respiratory tract infections are viral upper respiratory tract infections and bacterial respiratory infections.[21]

Sputum cultures were examined in outpatients for respiratory tract infections during the hajj season from 1991 to 1992. Three hundred and ninety-five samples were examined. Positive cultures were found in 118 specimens (30%); The most common pathogens found were *Haemophilus influenza, Klebsiella pneumonia, and Streptococcus pneumonia*. In the same study, 761 throat swabs were performed for virus examination, 20% of which were positive, especially influenza and adenovirus.[22]

High-density areas pose a risk of local outbreaks and the worldwide spread of infectious agents. The study was conducted on 566 patients of Hajj pilgrims in 1434H. Most of them (92%) suffer from respiratory symptoms.[23] Acute respiratory infections (ARI) are the leading cause of hospital admissions in Saudi Arabia during the Hajj season.[24]

In 2016, 2017 and 2018, the morbidity rate of Indonesian Hajj pilgrims due to a combination of various respiratory diseases was 49.0%, 51.95% and 49.31%, respectively. Meanwhile, in 2016, 2017 and 2018, the mortality rate of Indonesian Hajj pilgrims due to respiratory diseases was 27,5%, 30,7% and 36.8%, respectively.[25–27]

Elderly pilgrims are more susceptible to infectious diseases due to eating disorders, sleeping patterns, and damage to the immune system. In terms of nationality, the majority of infectious disease cases were discovered in Indonesian pilgrims (18.4%), Saudi pilgrims (17.1%), and Pakistani pilgrims (11.8%).[28]

CONCLUSION

About three million pilgrims come to the holy city of Mecca every year to perform the pilgrimage. The increasing number of pilgrims is accompanied by an increase in daily activities and transportation needs. As a result, large

amounts of solids, gases, microbes, and other pollutants are emitted into the air. Pollutants produced can cause various adverse effects on the health of pilgrims.

The respiratory tract is the main entrance point for air pollutants into the body. The effects of air pollution on respiratory tract diseases include an increase in asthma exacerbations, COPD and cystic fibrosis infections, hospital clinic visits, hospital emergency visits, hospital admissions, morbidity, and mortality. Every year, respiratory disease is one of the leading causes of illness and death among Indonesian pilgrims.

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