Vol. 5, No. 1, October 2024

e-ISSN 2474-1306

Official Journal of The Indonesian Society of Respirology

RESPIRATORY Science

Website: http://www.jurnalrespilogi.org

RESPIRATORY Science

Official Journal of The Indonesian Society of Respirology

Editorial Office
The Indonesian Society of Respirology
Jl. Cipinang Bunder, No. 19, Cipinang, Pulo Gadung
Jakarta Timur, Indonesia, 13240 Telp: 02122474845
Email: respirologyscience@gmail.com
Website: https://respiratoryscience.or.id/

Publisher
The Indonesian Society of Respirology

RESPIRATORY Science

Official Journal of The Indonesian Society of Respirology

VOLUME 5, NUMBER 1, October 2024

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Original Article

Correlation Between Changes in NLR Value and RECIST among Lung Cancer Patients at Saiful Anwar Malang Hospital

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Submitted: March 14th, 2024
Accepted: October 7th, 2024
Published: October 31st, 2024

Respir Sci. 2024; 5(1): 1-9
https://doi.org/10.36497/respirsci.v5i1.141

Abstract

Background: In practice, clinicians use Response Evaluation Criteria in Solid Tumors (RECIST) to decide the progressivity of lung tumors. Besides RECIST, there is an inflammatory marker called Neutrophil to Lymphocyte Ratio (NLR), which has prognostic value in cancer patients. Many previous studies have shown that NLR can predict the prognosis because inflammation in cancer patients is part of the tumor progressivity. Therefore, the changes in NLR value have the potency to be one of the ways to decide the progressivity of tumors in lung cancer patients.

Method: This cross-sectional study was conducted to see whether there is a correlation between RECIST and NLR in 95 lung cancer patients at Saiful Anwar Hospital whose data were taken from January 2022 to May 2023. The variable will be tested using the chi-square test to see the correlation and the logistic regression method to obtain the odds ratio.

Results: There is a significant correlation between changes in NLR and RECIST with P=0.041. Through Logistic Regression Analysis, the value of the odds ratio is 2.46 (CI 95%=1.03-5.94). In the group with progressive RECIST, the average NLR value after therapy was higher than the average NLR value after therapy in the non-progressive group.

Conclusion: This study concludes that changes in NLR value have the potency to help the determination process of lung cancer progressivity as RECIST does.

Keywords: lung cancer, lung cancer progressivity, NLR, RECIST

INTRODUCTION

Cancer has become one of the top health problems in the world. Especially in developing countries, such as Indonesia, it is estimated that there will be an increase in cases of cancer by 300% by 2030. In 2020, lung cancer became one of the most frequently fatal malignancy cases and had the highest incidence in Southeast Asia.[1] Based on the World Health Organization (WHO), lung cancer is the largest contributor to cancer

incidence in men. Apart from that, the Indonesia Ministry of Health also stated that 1/3 of cancer deaths in males are caused by lung cancer.[2]

In Indonesia, one of the main factors related to it is the smoking habit. The number of smokers in Indonesia is increasing, especially at the student age. Based on Global Youth Tobacco Survey Data, there are 32.1% of students who smoke in Indonesia. This smoking habit affects not only active smokers but also people around them, passive smokers, with an increased risk of lung cancer by 20-30%.[2]

Nowadays, one of the examinations that is used to diagnose lung cancer is the radiology examination. Computed Tomography Scan (CT-Scan) is one of the methods that is most commonly used.[3] CT- Scan is used to determine the stage of tumors, assess the mass of tumors, assess solitary lung nodules and others.[4]

CT-Scan is not only used for diagnostic but also to assess tumor development and evaluate patient therapy. Response Evaluation Criteria in Solid Tumors (RECIST) is the instrument to help the evaluation process of the CT-Scan result. The RECIST assessment will produce conclusions such as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD).[5]

Many studies have stated the relationship between inflammation and tumor growth. Systemic inflammation is associated with tumor growth factors such as angiogenesis, tumor growth, invasion and metastasis.[6] There is a marker used in assessing inflammation, called neutrophil-to-lymphocyte ratio (NLR). The neutrophil-to-lymphocyte ratio is a ratio value obtained from calculating the number of neutrophils and lymphocytes of the patient. According to Barret et al, the NLR is found to be higher in patients with cancer conditions.[7]

By looking at the correlation between NLR, as a marker of inflammation, and the role of inflammation, which is associated with the presence of tumors and their growth, an increase in NLR indicates an increase in inflammation which also indicates a worsening body condition due to tumor growth. The NLR test is relatively easy because it only uses the patient's complete blood test result.[8]

With the ease and practicality of NLR in the examination process, the changes of the NLR value could be another method, besides RECIST, in determining the disease progressivity of lung cancer patients. Another advantage is NLR also has a lower risk because there is no radiation effect provided by CT scans.

Many previous studies have discussed the role of NLR as a prognostic value but there are still no studies that discuss the correlation between changes in NLR values and RECIST. Therefore, this study was conducted to see the correlation between changes in NLR values and RECIST as an effort to help the process of determining the disease progressivity of lung cancer patients.

METHOD

This study is an analytic observational study with a cross-sectional approach. There were 95 subjects in this study and the data was obtained from the medical records of lung cancer patients at Saiful Anwar Hospital Malang from January 2022 to May 2023.

The inclusion criteria of this study were subjects who had complete NLR and RECIST data before and after therapy. While the exclusion criteria are subjects with incomplete data. The required data needed in this study are age, sex, neutrophil value, lymphocyte value, type of treatment, and RECIST result gained after one cycle of therapy. In this study, NLR was taken without considering other factors such as gender, age, comorbidities or other co-morbid conditions.

Subjects had a complete blood examination to obtain neutrophil and lymphocyte levels that will be calculated into a ratio. The result of the NLR examination before and after therapy will be compared and categorized into two categories, increased NLR and decreased NLR. It will also show the classification of the NLR value before and after therapy based on the normal value of NLR (0.78–3.52). The cut-off of the NLR was obtained from previous research by Forget et al which the range of NLR in healthy persons is 0.78–3.53.

Meanwhile, RECIST was obtained by comparing CT scan results before and after therapy. The conclusion of RECIST will be categorized into two categories, progressive categories (if the result obtained is Progressive Disease) and non-progressive categories (if the result obtained are Partial Response, Complete Response, or Stable Disease).

The data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS) application. Both variables will be tested using the chi-square test to see the relationship and the logistic regression method to obtain the odds ratio. If the analysis does not fulfill the chi-square analysis criteria, analyze statistics using Fisher exact tests.

RESULTS

From 95 subject data included in the inclusion criteria, the following characteristics were obtained in Table 1.

Table 1. Subject's Characteristics

Characteristics	N	%
Sex		
Male	62	65
Female	33	35
Age		
≥60	51	54
<60	44	46
Therapy		
Chemotherapy	85	89
Targeted Therapy	2	2
Chemotherapy + Radiotherapy	8	9

The average age of the subjects was 59 years and the male gender was the majority of the subjects of this study. There were 3 different types of therapy, the majority of subjects received chemotherapy and the rest received targeted therapy or a combination of

chemotherapy and radiotherapy.

Table 2. NLR Value Result and Changes

NLR Value	N	%
Before Therapy		
<0.78	3	3
0.78-3.53	41	43
>3.53	51	54
After Therapy		
<0.78	1	1
0.78-3.53	63	66
>3.53	31	33
NLR Changes		
Increase	31	33
Decrease	64	67

The result of the NLR test obtained before therapy showed that more than 50% of the subjects had a high NLR (>3.53) while after therapy 66% of the subjects had an NLR value of 0.78-3.53. The table also shows that 67% of subjects experienced a decrease in NLR after therapy.

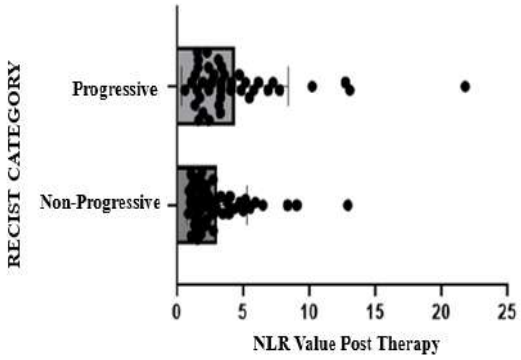
Table 3. RECIST Result (After Therapy) (n=95)

RECIST Result	N
Non-Progressive	
Complete Response	0
Partial Response	16
Stable Disease	38
Progressive	41

According to the RECIST data, after therapy, it showed that 54% of subjects had RECIST conclusions that included a non-progressive category while the rest were included in a progressive category.

The changes in the NLR value variable and RECIST variable were then processed using the chi-square method to produce correlation conclusions and using Logistic Regression to obtain the odds ratio.

Through the chi-square test, the significance value between changes in NLR values and RECIST result is P=0.041 which means there is a significant correlation between changes in NLR values and RECIST result. In addition, after calculating the odds ratio, it was found that OR=2.46 (95% CI=1.03-5.94), which means that patients with increased NLR have a likelihood of lung cancer 2.46 times more progressive than patients with decreased NLR.



Graphic 1. NLR Value After Therapy Data Distribution

Table 4. The Correlation between NLR Changes and RECIST

Variable	RECIST		P	OR (95% CI)
	Progressive	Non-Progressive		
Increased NLR	18	13	0.041	2.46 (1.03–5.94)
Decreased NLR	23	41		

Besides the correlation test, a graph was made to show the distribution of the NLR value after therapy. There is a difference in average NLR value after therapy, where in the progressive RECIST group, the average is 4.394 while in the non-progressive RECIST group, the average is 3.043.

DISCUSSION

From the data of this study subject, it was found that the majority of the subjects' age was above 60 with an average of 59.17. This is in line with the previous study which stated that ages >50 years have a higher risk of developing lung cancer than those <50 years. The age factor is important because, with increasing age, people will be exposed more to the risk factors of lung cancer along with decreasing immunity of the body and regeneration ability of cells.[9]

Other than age, based on the gender data, 65% of the subjects were male. Consistently, incidence and mortality data of lung cancer are found to be lower in women than men.[10] This is because men's smoking behavior is more often than women's, and smoking is the main cause of non-communicable diseases, especially lung cancer.[11]

However, nowadays there is a narrowing gap of smokers between the male and female category. There is a possibility that the mortality rate in women due to lung cancer may exceed men by 2045.[10] The incidence of lung cancer in the subject of this study is certainly not only associated with the risk factors of age and gender, many other factors may affect such as exposure to cigarette smoke, socioeconomic status and others.

One of the variables in this study is the change in NLR value. NLR is a marker that shows the innate immune response played by neutrophils and adaptive immunity plated by lymphocytes. Neutrophils have a role as the first line of the immune system when dealing with pathogens and have a major role when a systemic inflammatory response occurs.[12] Lymphocytes have an important role in suppressing tumor maturation through the process of immunity, one of which is by inducing apoptosis of cancer cells.[13]

In this study, it was found that 54% of subjects have NLR that exceeds normal limits (>3.53). This is in accordance with the results of a previous study which states that there is an increase in NLR in malignancy conditions because inflammatory conditions play an important role in its pathophysiology. Inflammation causes increased tumorigenesis.[12]

There is other proofs state that neutrophils can promote angiogenesis and tumor growth by inducing several factors such as the release of basic fibroblast growth factor, endothelial cell migration and production of reactive oxygen species.[13] However, after undergoing therapy, there was a decrease in the number of subjects who had high NLR (>3.53), which decreased from 54% to 33%. In contrast, there was an increase in subjects who have normal NLR (0.78-3.53)

from 43% to 66%. This is certainly related to the therapy that was given.

Three types of therapy were given to the subjects in this study. Among chemotherapy, radiotherapy combined with chemotherapy, and targeted therapy, the majority of subjects (89%) received chemotherapy. The goal of chemotherapy is to inhibit tumor proliferation and multiplication which will avoid invasion and metastasis. Chemotherapeutic agents generally affect the macromolecular synthesis and function of neoplasm cells by interfering with DNA, RNA, and protein synthesis.[14]

The next therapy is targeted therapy, 2 subjects of this study received targeted therapy which works by delivering drugs specifically to genes or proteins in cancer cells or tissues that support cancer growth.[15] The last type of therapy given to the 8 subjects of this study was a combination of chemotherapy and radiotherapy. This combination therapy is given to patients with good condition, minimal weight loss and elderly patients with severe comorbidities or contraindications to surgery.[14] Chemotherapy can help the radiotherapy process by shrinking the tumor before therapy and destroying the cancer cells that still exist after radiation therapy so that the therapy can work better.[16]

After receiving therapy, there were changes in the subject's blood profile. In this study, changes in blood profile can be seen from neutrophils and lymphocytes in the NLR value. In 67% of subjects who received chemotherapy, 100% of subjects who received combination therapy and 62% of subjects who received targeted therapy had a decrease in NLR.[13]

This decrease is possible because the administration of chemotherapy agents aims to reduce the growth or even eliminate the tumor, which is a source of chemotactic cytokines that will attract neutrophils to migrate to the tumor, causing an increase in neutrophils. Then the decrease in neutrophil production in the body can be reduced due to the absence of neutrophil chemotaxis activity.[13] In addition, chemotherapy itself affects the bone marrow, namely hematopoietic suppression. This effect will cause a decrease in blood cells, one of which is neutrophils.[17]

Although this study did not analyze the relationship of NLR with age and comorbid conditions, these factors also have an impact based on previous studies. Based on the study by Li et al on 3,262 healthy populations, the older age group tends to have a higher NLR value than the younger groups.[18]

This may happen since older people are more likely to be affected by chronic infections or malignant conditions, which as described earlier, increased inflammatory conditions can increase NLR as well. This reason may also explain the condition of increased NLR in people with comorbidities. On the other hand, the previous study shows that there is no significantly different NLR was found between the female and male population at each age group.[18]

This study states that there is a significant relationship between changes in

NLR values and RECIST. The role of RECIST in assessing the progression of lung cancer is very important because RECIST is a standard criteria rule that shows therapeutic response based on tumor growth or shrinkage through radiographic modalities that have been used globally. The results of RECIST can show the presence or absence of progressivity in tumor growth. By having a significant relationship with NLR, it can be said that changes in NLR values can predict the growth of lung tumors, whether progressive or not. Based on the results of the analysis, it was also found that an increased NLR was 2.46 times more likely to have a progressive result than a decreased NLR.[8]

In addition, after therapy, the group with progressive RECIST results had a higher average of NLR compared to the non-progressive group. These results are in line with various other sources that have stated the role of NLR as a predictor of cancer disease outcome. Based on a meta-analysis study, it was concluded that there is an association between poor prognosis and increased NLR in cancer patients.[8] Another similar study also stated that if the NLR value is >4 before therapy, it indicates poor Overall Survival (OS) and Progression-Free Survival (PFS) in lung cancer patients.[6]

The relationship between NLR and RECIST can be understood by looking at the role of neutrophils and lymphocytes, which indicate the inflammatory state in the body, especially due to tumors. In the case of malignancy, the increase of NLR is due to the development and spread of cancer.[13] With the presence of neutrophilia and/or lymphopenia in inflammatory conditions due to tumors, the NLR result will be higher. This inflammation itself is associated with various tumor growth factors, ranging from angiogenesis, progressiveness, and invasion to metastatic tumors.[6] Similarly, RECIST can also show tumor growth or shrinkage through radiographic modalities.

CONCLUSION

Among the 95 subjects of this study, lung cancer patients at Saiful Anwar Hospital Malang, 54 of them had non-progressive RECIST conclusion results Complete Response/Partial Response/ Stable Disease (CR/PR/SD) after undergoing therapy, while 41 of them had progressive results. Then, 64 subjects had a decrease in NLR value after therapy and the remaining 31 had an increase in NLR value.

Based on these two types of data, it was found that there was a significant relationship between changes in NLR values and RECIST in lung cancer patients at Saiful Anwar Hospital Malang. It was found that subjects with increased NLR had a likelihood of lung cancer 2.46 times more progressive than patients with decreased NLR. This result is also supported by previous journals that examine the role of NLR as a prognosis value in cancer patients.

Further research is needed to determine the NLR cut-off value used to

assess the progressivity of lung cancer patients and can be used for further research on NLR in lung cancer patients. In addition, future studies are needed to have more specific subjects such as patient age, patient lung cancer stage and patient therapy data.

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Original Article

The Relationship of Serum Zinc Levels and Clinicopathological Characteristics in Individuals with Lung Cancer

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Submitted: April 12th, 2024
Accepted: October 7th, 2024
Published: October 31st, 2024

Respir Sci. 2024; 5(1): 10-8
https://doi.org/10.36497/respirsci.v5i1.143

Abstract

Background: Lung cancer is one of the main contributors to malignancy and leads to the patient's death. The immune system, genetics, and inflammation affect lung cancer progression. Zinc (Zn) is an essential mineral; a Zn deficiency increases the tumor suppressor's expression, damaging deoxyribonucleic acid (DNA) repair ability in tumor growth. The study focused on establishing a relationship between serum Zn levels and lung cancer patients' clinicopathologic characteristics.

Method: Thirty-five patients diagnosed with lung cancer were part of the study. The study collected clinicopathological data and serum Zn levels at the initial diagnosis. Serum Zn insufficiency is characterized by a below 80 µg/dL serum Zn level.

Results: The median Zn level in our study was 65 µg/dL (range=56.5-73 µg/dL). Serum Zn deficiency was observed in 91.4% of patients, particularly those who had a smoking history, advanced stage, or had hypoalbuminemia. The low-level group exhibited significantly lower albumin concentrations (3.06 g/dL vs. 3.66 g/dL; P=0.024) than the normal group.

Conclusion: Most patients with lung cancer at initial diagnosis had a deficiency in Serum Zn, which was associated with hypoalbuminemia.

Keywords: clinicopathological characteristic, hypoalbuminemia, lung cancer, serum Zn level

INTRODUCTION

The International Agency for Research on Cancer (IARC) projects reported that in 2020, 19.3 million new cases of cancer globally, resulting in approximately 10 million deaths linked to cancer. In Indonesia, the increasing trend in cancer incidence is evident, with over 1.3 million cases treated in 2016 alone.[1] According to data from the Global Cancer Observatory, there were an anticipated 396,914 new cancer diagnoses in

Indonesia in 2020, with a corresponding death toll of 234,511. As per the 2018 Riset Kesehatan Dasar (RISKESDAS) report by Indonesia Basic Health Research, the country's cancer prevalence has increased from 1.4 per 1000 people in 2013 to 1.8 per 1000 people in 2018.[2]

Lung cancer, accounting for approximately 1.8 million fatalities and 2 million diagnoses globally, is the leading contributor to death due to cancer. Lung cancer is one of the common cancer diagnoses for both men and women. There is a global increase in lung cancer cases attributed to the growing availability of tobacco and industrial development in developing nations.[3] One of the most critical factors related to this increase in morbidity and mortality was the parallel increase in cigarette consumption after World War II.[4]

Tobacco use is considered the most significant lung cancer risk, with 80-90% of the total number of cases in the world related to cancers emitted as primary or secondary smoke. However, it is not the only risk factor.[4] Previous research has established that certain external factors, diet, and exercise can impact the likelihood of developing lung cancer. Nevertheless, specific concentrations of trace elements like zinc (Zn) and copper may impact lung cancer progression.[5]

Zinc is crucial in controlling different physiological and biochemical conditions in organisms. It is pivotal in preserving cell membrane integrity and protein, carbohydrate, and lipid metabolism. It also supports the immune system, wound healing, and various biological processes linked to growth and development. Zinc deficiency impacts many hormones' physiological and biochemical levels.[6]

Zinc ions play a role in structural and regulatory proteins, such as transcription factors, and are involved in forming "Zn fingers" that enable transcription factors to bind to deoxyribonucleic acid (DNA). When Zn ions interact with these biological systems, they form a pool involved in the specific functions of the proteins present. Given the numerous functions carried out by this component, it is crucial in safeguarding against tumor initiation and promotion. However, the mechanism of this function remains not fully understood.[7]

There is an increasing amount of evidence suggesting a connection between Zn deficiency and cancer. Multiple epidemiological studies have suggested that a lack of Zn raises the chances of developing cancer. Research has linked Zn deficiency with larger tumor size and advanced tumor stage among individuals with head and neck cancer.[8,9]

According to the findings of a meta-analysis conducted by Wang et al, blood Zn levels were found to be considerably lower in lung cancer patients in contrast to levels found in controls.[5] The antitumor activity of Zn involves several functions, including DNA damage and repair, oxidative stress, immune function, and inflammation. Insufficient Zn levels may alter the antioxidant defense mechanism and hinder the immune system's function.[8]

While there have been studies indicating reduced Zn concentrations in the serum of patients suffering from several kinds of cancers, there is an inconsistency in the results. Moreover, there appears to be a gap in research regarding the relationship between Zn status and lung cancer in developing countries such as Indonesia. This study intended to explore the prevalence of serum Zn insufficiency in patients diagnosed with lung cancer and assess the relationship between clinicopathological characteristics and the patient's blood Zn levels.

METHOD

Cross-sectional research was undertaken with 35 participant patients at the Doris Sylvanus Hospital in Palangkaraya from January to April 2023. The study's criteria for inclusion were patients with lung cancer diagnosis, aged 18 or older, who had not undergone surgery, radiation, or chemotherapy, and who were willing to participate by signing an informed permission form. The exclusion criteria encompassed any other form of malignancy and any medical problems that are known to impact anemia, such as individuals with existing or previous hematology-related conditions, chronic renal disease, and chronic liver disease. This research received permission from the Ethics Committee of Doris Sylvanus Hospital No. 784.1/UM-TU/RSUD/01-20.

Age, gender, smoking history used Brinkman index, height, body weight (BW), body mass index (BMI), main symptoms, clinical stage, metastasis, and histology were analyzed as patient characteristics. Leucocyte, hemoglobin level, thrombocyte, total lymphocyte counts (TLC), absolute neutrophil count (ANC), neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), albumin (Alb), and serum level of Zn were among the laboratory parameters measured. As per Japan's Practical Guidelines for Zn Deficiency, Zn concentration in the serum below the 80 µg/dL threshold indicates a serum Zn deficiency. Serum Zn levels were categorized into "deficient" and "normal" groups.

Variables that adhered to a normal distribution were represented using means and standard deviations. In contrast, medians and interquartile ranges represented variances that deviated from a normal distribution. The mean values of the patient groups were compared using the student t-test or Mann-Whitney U test for continuous data. The Fischer exact test is used to identify any significant differences among categorical variables. Statistical analysis was performed using SPSS 22 software, and statistical significance was assessed at a significance level of $P>0.05$.

RESULTS

Table 1 shows the clinical features of the 35 individuals diagnosed with lung cancer. The study sample consisted of eight female and 27 male participants, with a median age of 60. The median Zn level

was 65 µg/dL, ranging from 56.5 to 73 µg/dL. Eight of the patients were non-smokers, whereas 27 had a smoking history.

Table 1. The Clinical Features Exhibited by Individuals Diagnosed with Lung Cancer

Variable	n = 35
Age (years), median (range)	60 (53-68)
Sex	
Male	27 (77.1%)
Female	8 (22.9%)
History of smoking	
Smoker	27 (77.1%)
Brinkman Index <600	18 (66.7%)
Brinkman Index ≥600	9 (3.3%)
Non-Smoker	8 (22.9%)
Main Symptom	
Cough	13 (37.1%)
Shortness of breath	9 (25.7%)
Chest Pain	13 (37.2%)
Body Mass Index (kg/m^2)	
<18.5	24 (68.6%)
≥18.5	11 (31.4%)
Pathology	
Adenocarcinoma	19 (54.3%)
Squamous cell	13 (37.1%)
SCLC	3 (8.6%)
Stage	
<IV	6 (17.1%)
≥IV	29 (82.9%)
Metastasis	
No metastasis	6 (17.1%)
Intrathoracic metastasis	27 (77.2%)
Extrathoracic metastasis	2 (5.7%)
Laboratory parameter	
Hemoglobin (g/dl), median (IQR)	11.7 (10.2-13)
Leucocyte (uL), median (IQR)	12330 (8460-16320)
ANC ($/mm^3$), median (IQR)	8340 (6000-13630)
TLC ($/mm^3$), median (IQR)	1787 (1337-2384)
Thrombocyte ($x10^{9/L}$ mg/dl), median (IQR)	375 (279-465)
CRP (mg/dL), median (IQR)	87.77 (16.53-116.23)
Albumin (g/dL), median (IQR)	3 (2.8-3.42)
Zn level (µg/dL), median (IQR)	65 (56.5-73)

Note: SCLC=Small Cell Lung Cancer; ANC=Absolute Neutrophil Count; TLC=Total Lymphocyte Count; CRP=C-Reactive Protein; IQR=interquartile range

Table 2. The Clinical Presentation of the Patient Diagnosed with Lung Cancer is Determined by Analyzing the Serum Zn Levels

Variable	Serum Zn level		P
	Low level (n=32) (< 80µg/dL)	Normal level (n=3) (≥80µg/dL)	
Age, median (range), years	58.88±9.8	59.33±2.08	0.937 ª
Sex			0.124ᵞ
Male	26	1	
Female	6	2	
History of smoking			0.124ᵞ
No	6	2	
Yes	26	1	
Brinkman Index			1.000ᵞ
<600	9	0	
≥600	17	1	
Body mass index			0.190ᵞ
< 18.5	8	2	
≥ 18.5	24	1	
Pathology			0.500 ᵞ
Adenocarcinoma	16	3	
Squamous cell	3	0	
SCLC	13	0	
Stage			1.000ᵞ
<IV	6	0	
≥IV	26	3	
Metastasis			1.000ᵞ
No	7	0	
Yes	25	3	
ANC (/mm^3)	8460 (5995-12479)	6936 (6723-10983)	0.724ᵝ
TLC (/mm^3)	1767 (1351-2482)	1860 (1555-1970)	0.953ᵝ
NLR	3.89 (3.44-8.13)	3.5 (3.33-3.5)	0.859ᵝ
CRP (mg/dL)	90.61 (18.06-118.12)	61.9 (38.94-81.23)	0.680ᵝ
Albumin (g/dL)	3.06±0.43	3.66±0.31	0.024ª*
Zn level (µg/dL) (median)	63.5 (35-79)	101 (89-105)	

Note: *significant P<0,05; ªStudent T-test; ᵝMann Whitney; ᵞFisher exact; ANC=Absolute Neutrophil Count; TLC=Total Lymphocyte Count; NLR=Neutrophil Lymphocyte Ratio; CRP=C-Reactive Protein

Thirteen patients experienced the main symptom of coughing, nine patients experienced shortness of breath, and another thirteen patients claimed chest pain. As much as 68.6% of patients were underweight with a BMI <18.5. Three individuals were found to have small cell lung cancer (SCLC), thirteen with squamous cell carcinoma, and nineteen with adenocarcinoma. Our studies reported most patients at stage IV, with 27 having metastasis intrathoracic and 2

having metastasis extrathoracic.

Thirty-two patients were affected by serum Zn deficiency, accounting for 91.4% of the total cases. The clinical features of lung cancer patients based on their serum Zn levels are detailed in Table 2. The median blood Zn level in the low-level group was 63.5 µg/dL, with a range of 35–79 µg/dL. In the normal-level group, the median serum Zn level was 101 µg/dL, with a range of 89–105 µg/dL.

Individuals who have a smoking background, high Brinkmann index, at stage IV, and with metastasis showed predominantly low Zn levels. Compared to the normal group, the albumin levels in the low-level group were significantly lower (3.06 g/dL vs. 3.66 g/dL; P=0.024). There were no notable variations between the two groups regarding age, sex, smoking history, Brinkman index, BMI, pathological type, stage, metastasis, ANC, TLC, NLR, and CRP.

DISCUSSION

We discovered that 91.4% of the patients with lung cancer had low serum Zn (< 80µg/dL). Several studies conducted in recent years have provided evidence that Zn shortage and lung cancer are related to one another. According to Wang et al, in European and Asian populations, lung cancer patients showed significantly lower serum Zn levels compared to controls.[5]

According to Bai et al, there is a possibility that Zn could be used to help prevent lung cancer. Research has indicated that elevated levels of Zn in the bloodstream may decrease the likelihood of developing lung cancer by potentially affecting telomere events and the expression of specific oncogenes.[10]

Lung cancer is considered predominantly a smoking-related disease, similar to our research finding that most of our patients were smokers (77.1%) and had low levels of Zn serum compared to non-smokers, especially in the high Brinkman index. In the present study, the median serum Zn levels at initial lung cancer diagnosis were 65 (56.5-73) µg/dL, and the majority were in an advanced stage. Compared to the average of 87.5±11.2 (65-110) µg/dL, the serum Zn levels in individuals with lung cancer were 22.5 µg/dL lower than the reference value for a healthy human body.[11]

Similar to recent meta-analyses by Wang et al, blood zinc levels were considerably lower in patients than in control. Meanwhile, Zhang et al discovered that patients with lung cancer had a significantly higher serum copper/zinc ratio (indicating low zinc levels) than patients with healthy controls; additionally, patients with advanced lung cancer had a significantly higher ratio than those with early-stage lung cancer.[12] The decreased Zn consumption may have diminished Zn levels in individuals with lung cancer. Nevertheless, animal and human bodies can regulate Zn levels within a wide range of Zn intake, ensuring homeostasis. The ability to change may be altered when a cancer progresses.[13]

Moreover, in the process of cancer progression, tissue injury is recognized to

release naturally occurring substances from white blood cells called polymorphonuclear leukocytes. As a blood result, Zn levels decrease, and the liver absorbs more Zn. The increased uptake from the bloodstream can be attributed to lung cancer cells having a significantly greater Zn metabolism requirement than healthy cells.[13]

Reduced levels of Zn in the blood might occur due to ongoing inflammation, a common characteristic of lung cancer. The diminished involvement of Zn in the immune system and antioxidant response can expedite cancer progression if there is a decrease in Zn levels. It could potentially result in a self-perpetuating cycle.[13]

Increased endogenous and external oxidative insults can harm the lungs. Numerous investigations have shown a clear correlation between redox imbalance, both locally and systemically expressed, and lung cancer. A physiological imbalance favoring oxidants (free radicals or reactive species) over antioxidants can lead to oxidative stress, a phenomenon or disease that affects cells.[14]

Telomeres, consisting of repeating DNA sequences, are highly conserved structures at the distal ends of eukaryotic chromosomes. Telomeres keep chromosomal ends from breaking down and fusing, crucial for preserving structural integrity and genetic stability.[15,16]

According to reports, telomere shortening has been linked to inflammation and oxidative stress. Life expectancy was significantly reduced by telomere shortening, which raised the risk of age-related chronic illnesses and even malignancies. Zn is a vital trace mineral in food with potent anti-inflammatory and antioxidant effects. Though the fundamental process remains unclear, there are a few plausible hypotheses. Zn may promote genomic integrity, lower oxidative stress and inflammatory reactions, and increase telomerase activity to sustain telomere length.[15]

This investigation also revealed a strong positive association between serum albumin and Zn levels. Albumin is essential for the systemic distribution of Zn since it is the primary carrier of Zn in plasma.[17] Albumin binds around 80% of blood Zn; a positive correlation exists between albumin and serum Zn levels. Additionally, hypoalbuminemia makes less Zn bound to albumin in the blood, which increases Zn excretion in the urine.[18]

Meanwhile, tumor necrosis factor might make the microvasculature more permeable, facilitating more albumin transcapillary transit. In the initial stages of cancer, there is usually a mild or no decrease in the albumin levels. However, as the disease progresses, there is a significant fall in albumin levels, which can be used as reliable indicators of the prognosis of cancer.[19,20]

This study also comes with limitations. The research was conducted in one center with a limited sample, and underlying health conditions that could potentially impact the levels of trace elements, like infectious diseases, were not considered. Therefore, it is necessary to

conduct larger multicenter studies to confirm our findings.

CONCLUSION

Based on this study, it can be concluded that individuals diagnosed with lung cancer often have low levels of Zn in their bodies. Furthermore, much data indicates a strong connection between the amounts of Zn in the blood and serum albumin levels. Insufficient nutrition at the time of diagnosis may have influenced this outcome. Further investigation is required to authenticate and revise our conclusions regarding patients with lung cancer.

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Original Article

Profile of Risk Factors for Venous Thromboembolism (VTE) in Acute COPD Exacerbations at Kolonel Abundjani Bangko Regional Hospital

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Submitted: May 8th, 2024
Accepted: October 22nd, 2024
Published: October 31st, 2024

Respir Sci. 2024; 5(1): 19-27
https://doi.org/10.36497/respirsci.v5i1.151

Abstract

Background: Acute exacerbation of COPD is characterized by dyspnea and/or cough with worsening sputum production for <14 days. Patients with acute exacerbations of COPD are at increased risk of vascular events, including venous thromboembolism (VTE). VTE risk factor assessment can be carried out using a scoring system to estimate the risk of a patient experiencing VTE before further examination is conducted.

Method: This study used a cross-sectional approach. Research subjects were selected from patients diagnosed with acute exacerbation of COPD at Kolonel Abundjani Bangko Regional Hospital from November 2023 to January 2024. Patient data were extracted from medical records, and then patients who were compatible with the inclusion criteria were interviewed using the Wells and Padua criteria**.** Univariate analysis was conducted to assess the characteristics of VTE risk in acute exacerbation of COPD. Bivariate analysis was utilized to determine the correlation between the exacerbation of COPD and VTE risk using the chi-square test.

Results: A total of 20 cases of acute exacerbation of COPD were identified from November 2023 to January 2024. Based on Wells's criteria, as many as 18 patients (90%) were not at risk of developing VTE. Based on Padua criteria, 13 patients (65%) were at low risk and 7 patients (7%) were at high risk of developing VTE. The most common patient characteristics based on the scoring system are an increase in heart rate >100x according to the Wells criteria and the presence of acute infections or rheumatological disorders, which represent the Padua criteria. There is no correlation between acute exacerbation of COPD and VTE risk scoring.

Conclusion: The majority of patients with acute exacerbation of COPD are not at risk of developing VTE. There is no correlation between acute exacerbation of COPD and the risk of VTE.

Keywords: acute exacerbation of COPD, venous thromboembolism (VTE), Wells criteria, Padua criteria

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality, which increases the economic and social burden quite significantly.[1] Based on data from the World Health Organization (WHO), COPD is the third cause of death, with a total of 3.23 million deaths worldwide in 2019.[2]

Acute exacerbation of COPD (AECOPD) is characterized by dyspnea and/or cough with worsening sputum production for <14 days. These onsets are usually associated with local and systemic inflammation caused by respiratory tract infections, pollution, and other causes that impact the lungs. Based on guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023, AECOPD is classified based on the degree of severity, which consists of mild, moderate, and severe.[1]

Hospitalized patients with acute exacerbations of COPD are at increased risk of vascular events, including venous thromboembolism (VTE), which is more commonly known as a manifestation of deep vein thrombosis (DVT) and pulmonary embolism (PE).[3]

COPD was assessed as a moderate risk factor for VTE. In previous research, it was found that COPD patients who suffered from VTE had a two-times higher risk of death than those who suffered from VTE without COPD. About 50% of stage III/IV COPD patients die within 3.5 months after the VTE event. Several risk factors for VTE in COPD patients include immobilization, bronchial superinfection, right ventricular failure, and venous outflow stasis.[3,4]

Assessment of VTE risk factors in patients can be carried out using a scoring system, which makes it easier to stratify patients in estimating the patient's risk of developing VTE before further examination is carried out. So far, VTE risk factor scoring has been approved by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), some of which include Wells criteria and Padua criteria.[5]

Based on a review of the existence of vascular risk factors, especially in patients with AECOPD, as well as the limited research related to this in Indonesia, the researchers were interested in examining the risk profile of VTE events in patients with AECOPD at Kolonel Abundjani Bangko Regional Hospital, which is one of the hospitals in Merangin Regency, Jambi, Indonesia.

METHOD

This was a descriptive observational study with a cross-sectional approach taken from patients diagnosed with AECOPD at the Kolonel Abundjani Bangko Regional Hospital. The research sample included all patients with AECOPD who were admitted to Kolonel Abundjani Regional Hospital from November 2023 to January 2024. Researchers excluded patients with AECOPD who refused to be interviewed.

Patients' data were taken from medical records and those who met the

inclusion criteria were then interviewed using the Wells and Padua criteria. The data and scoring results were recorded and collected using Microsoft Excel and analyzed using Statistical Product and Science Service (SPSS) 26th version. Data analysis and presentation were processed using univariate analysis to assess the characteristics of VTE risk in AECOPD. Bivariate analysis was utilized to determine the correlation between AECOPD and VTE risk using the Chi-Square test.

RESULTS

There were 20 cases of AECOPD during November 2023–January 2024 that met the inclusion and exclusion criteria.

Table 1. Characteristic of AECOPD at Kolonel Abundjani Bangko Regional Hospital (N=20)

Characteristics	N (%)
Gender	
Male	19 (95%)
Female	1 (5%)
Age	
56 – 65 years	11 (55%)
>65 years old	9 (45%)
Smoking History (Brinkman Index)	
Mild smoker	0 (0%)
Moderate smoker	1 (5%)
Heavy smoker	19 (95%)
Modified Medical Research Council Scale	
0	0 (0%)
1	0 (0%)
2	0 (0%)
3	15 (75%)
4	5 (25%)
Classification of Exacerbations (Anthonisen)	
Type I Exacerbation	15 (75%)
Type II Exacerbation	3 (15%)
Type III Exacerbation	2 (10%)

Table 1 shows the characteristics of AECOPD patients at Kolonel Abundjani Regional Hospital. Based on gender, 19 patients (95%) were male and 1 (5%) was female. The age of the patients was predominantly over 55 years, with 11 people (55%) in the range of 56–65 years old and 9 people (45%) in the range >65 years. A total of 19 (95%) AECOPD patients were classified as heavy smokers, and only 1 patient (5%) was classified as a moderate smoker.

Based on the Modified Medical Research Council Scale (mMRC), all respondents (100%) were at mMRC level ≥2. Based on the classification of exacerbations, as many as 15 patients (75%) had type I (severe) exacerbations, 3 patients (15%) had type II (moderate) exacerbations, and 2 patients (10%) had type III (mild) exacerbations. Patients with AECOPD were grouped based on the results of the risk of VTE events using the Wells and Padua criteria.

Table 2. Risk assessment of VTE using Wells score (PE and DVT) (N=20)

Wells Criteria	N (%)
PE	
Unlikely	18 (90%)
Likely	2 (10%)
DVT	
Unlikely	18 (90%)
Likely	2 (10%)

If the results of Wells criteria (PE) >4, then there is a risk of causing PE. Table 2 shows that 18 people (90%) were not at risk of PE, and 2 people (10%) were at risk of PE.

Table 3. VTE risk criteria based on Wells score (PE and DVT)

Wells Criteria	N (%)
PE	
Heart rate >100x/m	11 (55%)
Alternative diagnoses other than PE/DVT are unlikely	0 (0%)
Hemoptysis	0 (0%)
History of cancer	0 (0%)
History of immobilization or surgery	5 (25%)
History of DVT/PE	0 (0%)
Clinical signs and symptoms of DVT (leg edema and pain on palpation of deep vein)	2 (10%)
DVT	
Active cancer	0 (0%)
Paralysis, paresis of lower limbs	0 (0%)
History of bed rest 3 days or major surgery 4 weeks	5 (25%)
Swelling of the entire leg	0 (0%)
Swelling in deep vein distribution area	0 (0%)
Swelling >3 cm compared to asymptomatic leg	2 (10%)
Pitting edema	2 (10%)
History of DVT	0 (0%)
Non-varicose superficial collateral veins	0 (0%)
Alternative diagnosis is at least as likely	0 (0%)

In assessing the risk of DVT, a Wells score of ≥2 is considered to be at risk of causing DVT. About 18 patients (90%) were not at risk of DVT, and 2 patients (10%) were at risk of DVT.

In Table 3, it was found that the risk characteristics of VTE based on Wells score (PE) in patients included: heart rate >100x/minute that was found in 11 patients (55%), immobilization that was observed in 5 patients (25%), and 2 patients with signs and symptoms of DVT (10%).

Characteristics of patients with AECOPD based on Wells score (DVT) are shown in Table 3. A total of 5 patients (25%) had a history of immobilization, 2 patients (10%) had swelling in the legs >3 cm compared to the legs without complaints, and 2 patients (10%) had pitting edema.

Another criterion that can be used for assessing the risk of VTE events is the Padua criteria; if the scoring result is ≥4, the patient is at high risk of developing VTE. Table 4 shows that 13 patients (65%) are at low risk, and 7 patients (35%) are at high risk.

Table 4. Risk assessment of VTE using Padua score (N=20)

Padua Criteria	N (%)
Low risk	13 (65%)
High Risk	7 (35%)

Based on the Padua scoring assessment in Table 5, five patients (25%) had a history of bed rest ≥3 days, 6 patients (30%) had thrombophilia, 8 patients (40%) were over 70 years old,

respiratory/heart failure was found only in 1 patient (5%), acute infections and/or rheumatological disorders in 2 patients, and obesity (BMI ≥30 kg/m^2) was observed in 2 patients (10%).

Table 5. Characteristics of VTE Risk Factor using Padua criteria

Padua Criteria	N (%)
Alternative diagnoses other than PE/DVT are unlikely	0 (0%)
Cancer History	0 (0%)
Bed rest ≥3 days	5 (25%)
Thrombophilia	6 (30%)
Age ≥70 years	8 (40%)
Respiratory/heart failure	1 (5%)
Acute myocardial infarction and/or ischemic stroke	0 (0%)
Acute infection and/or rheumatological disorders	13 (65%)
Obesity (BMI ≥30 kg/m^2)	2 (10%)
Hormonal therapy	0 (0%)

Based on the chi-square test, there is no correlation between AECOPD and the risk of VTE using Wells criteria, with a value of P=0.690. Also note the correlation between AECOPD and the risk of VTE using Padua criteria, there is no correlation with a value of P=0.896 (Tabel 6).

Table 6. Correlation between AECOPD and VTE risk using Wells criteria and Padua criteria (N=20)

Correlation of VTE risk and AECOPD	P
using Wells criteria	0.690*
using Padua criteria	0.896*

Note: *chi-square tests

DISCUSSION

Based on the characteristics of AECOPD patients, there were more male patients (95%) than females (5%). These are following studies conducted by Zhang et al in China, which stated that 64.2% of COPD patients were male, while 35.8% were female.[6]

Even though it is generally considered that COPD disease occurs in older men, the prevalence of COPD continues to increase in women in line with the high smoking rate.[7] Based on data from the Centers for Disease Control and Prevention (CDC) from 2011 to 2020, it was found that in adulthood, the prevalence of COPD in women was higher than in men.[8]

Based on age, the largest age group was the 50–65 years range in 11 patients (55%), while 9 patients (45%) were in the age range >65 years. The prevalence of COPD is two to three times higher at age 60 than at younger ages. As age increases, a progressive decline in lung function is found, including a decrease in FEV_1 of around 20 ml/year, followed by a decrease in FEV_1/FVC and an increase in residual volume with persistent lung capacity. These changes in lung function cause a decrease in oxygen levels and the ability to eliminate CO_2 due to a decrease in compliance lungs and elasticity recoil lungs.[9]

The smoking history of patients with AECOPD was measured based on the Brinkman Index, and it was found that 19 patients (95%) had a history of being heavy smokers. Based on studies conducted by Au, tobacco smoke is a potent stimulant in triggering inflammation and increasing the risk of exacerbations.[10] In line with this research, Dahl et al also noticed that increased concentrations of

CRP, a marker of inflammation, were associated with an increased risk of exacerbations and death in COPD.[11]

Based on evaluation using mMRC, all patients were at mMRC level ≥2. Dyspnea is the most disturbing complaint and causes activity limitations in COPD patients. The mMRC is used to measure degrees of dyspnea that is associated with daily activities. mMRC ≥2 is used as a cut-off for severe symptoms.[12]

In COPD, there are thickening of the bronchial walls and a reduction of elastic fibers, which cause bronchial collapse and increase hyperinflation and dyspnea. Perez explained that there was a significant relationship between the level of exacerbations on the mMRC scale.[13]

Anthonisen described COPD exacerbation as an acute and ongoing disorder that included at least 2 of these symptoms: dyspnea, an increase in sputum volume, and a change in sputum color.[14] Based on this research, it was found that, according to the Anthonisen Classification, the highest degree of exacerbation was type I (75%).

Patients with AECOPD were then interviewed using risk factor scoring using Wells criteria. Based on Wells's criteria, the incidence of PE and DVT each had the same results. About 18 patients (90%) were not at risk, and 2 patients (10%) were at risk of developing PE and DVT. These results are supported by a study conducted by Gunen et al which stated that as many as 16% of COPD exacerbation patients were confirmed to have VTE as a complication or trigger factor after going through screening using the Wells criteria and confirmed via CT angiography examination.[15]

PE can worsen symptoms in COPD patients, although it is very difficult to distinguish it from other causes of exacerbation by clinical criteria. The prevalence of PE in patients with AECOPD ranges from 0 to 29%; this figure cannot be determined with certainty due to the limited number of studies related to this research.[15] DVT has a much lower prevalence in patients with AECOPD, ranging from 1.6 to 12.7%.[16]

Based on the assessment of acute COPD exacerbations using the Padua scoring, more patients (65%) were at low risk than those with high risk (35%) of developing VTE. Based on GOLD 2023, thromboprophylaxis therapy should be given to patients with AECOPD who are hospitalized at high risk.[1]

Furthermore, an analysis of the characteristics of the risk of VTE was carried out in patients with AECOPD. The highest risk of VTE was heart rate >100 times/minute in as many as 11 patients (55%) which represented the Wells (PE), and acute infection and/or rheumatology in as many as 13 patients (65%) representing the Padua criteria.

A study conducted by Warnier et al concluded that increased heart rate was a strong and independent risk factor for all causes of death in patients diagnosed with COPD, but there was no significant relationship between heart rate and other respiratory complications such as exacerbations and pneumonia in COPD

patients. In general, patients with COPD have a higher heart rate than patients without COPD. This is due to the risk of endothelial dysfunction caused by smoking, which triggers autonomic dysfunction due to tissue hypoxemia.[17]

The main cause of AECOPD is infection. Around 40–60% of cases are caused by bacterial infections, 30% are caused by viruses, and 5-10% are caused by atypical bacteria. COPD patients experience disturbances in the lung defense mechanism, as a consequence causing the proliferation of PPB (potentially pathogenic bacteria) and increasing bronchial secretions.[18]

In a retrospective study comparing the effectiveness of VTE risk assessment scoring, it was found that, in general, the Wells score was superior to the Padua score in predicting the risk of developing VTE. Wells's score had modifiable risk factors for VTE events, such as hemoptysis and heart rate that could reflect the status quo of patients when entering treatment, whereas the Padua score did not include this criteria.[5] Based on a cohort study conducted in China, Yang et al concluded that the Padua predictive score might not be appropriate to predict VTE risk in hospitalized patients with acute respiratory conditions.[19]

Although AECOPD increases the risk of vascular events, including VTE, our study shows that there is no correlation between AECOPD and the risk of VTE. Based on a previous study from Sadeghi et al, it was indicated that using Wells criteria based on the patient's condition was not an appropriate diagnostic tool for PE; it is necessary to combine different measurements of D-dimer level to provide a more accurate diagnostic protocol for PE.[20]

Currently, there are few studies on the prevalence of VTE among patients with acute exacerbations of COPD, particularly using VTE risk scoring to investigate. Most studies assessed VTE using suitable examination tools such as D-dimer and CT angiography. Considering the small number of our patients and limited reliable examinations in our hospital, these may affect the results of our study. Hence, further research to improve our limitations is warranted.

CONCLUSION

The characteristics of COPD patients with acute exacerbations at the Kolonel Abundjani Bangko Regional Hospital are dominated by males, age range of 56-65 years, a history of heavy smoking, and admission to the hospital with type I exacerbation. The most common clinical symptoms of VTE are an increase in heart rate >100x/minute and the presence of an acute infection that precedes the onset of an exacerbation in the patient.

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Original Article

The Relationship between Particulate Matter and Length of Exposure to Respiratory Complaints and Lung Function Disorder among Brick Craftsmen in Aceh Besar

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Submitted: September 17th, 2024
Accepted: November 18th, 2024
Published: November 28th, 2024

Respir Sci. 2024; 5(1): 28-39
https://doi.org/10.36497/respirsci.v5i1.161

Abstract

Background: Brick craftsmen are heavily exposed to particulate matter (PM) from brick burning, possibly contributing to respiratory complaints. The research aims to evaluate the association between PM levels, duration of exposure, respiratory complaints, and lung function disorders among brick craftsmen in Aceh Besar.

Method: The research method is observational analytic with a cross-sectional design. It was conducted in September 2023 on 68 respondents to assess lung function using spirometry and PM levels using the Air Quality Monitor.

Results: The data analysis revealed restrictive types of lung function disorders (47.1%), 75% of participants had worked for more than three years with working hours ≥8 hours/day (100%), the most frequent respiratory complaint was coughing (23.5%) and shortness of breath (13.2%), and the dominant type of work was brick molding (67.6%) rather than burning (32.4%). The PM2.5 index in the brick manufacturing area is classified as very dangerous (100%), while the PM10 index is identified as very unsafe (55.6%) and very dangerous (44.4%). The correlation analysis revealed a significant connection between PM2.5 as well as PM10 and lung function impairments (values of P=0.002 and 0.012, respectively). There was a significant correlation between work periods and lung function impairments (P=0.037). Multivariate analysis showed that a working term of 1-3 years was strongly linked with lung function disorder (FEV_1) among brick craftsmen in Aceh Besar (P=0.026).

Conclusion: This study showed that PM exposure was significantly associated with impaired lung function but not with respiratory complaints. Furthermore, a long working period is significantly associated with respiratory symptoms, especially for workers with 1-3 years, and is associated with impaired lung function in brick artisans in Aceh Besar.

Keywords: length of exposure, lung function disorder, particulate matter (PM), respiratory complaint

INTRODUCTION

Air pollution poses a significant global health challenge, with detrimental effects on respiratory function, especially in low- and middle-income countries.[1] According to the World Health Organization (WHO), air pollution accounts for over 7 million deaths annually, with most occurring in low- and middle-income nations.[2]

Exposure to air pollution has been linked to impaired lung function, particularly in people who are exposed continuously for an extended time.[3] Air pollution may arise both outdoors and indoors. A common source of outdoor air pollution comes from industrial fields, such as brick factories.[4]

The brick manufacturing industry is a significant source of air pollution due to particulate emissions from burning bricks during production.[5] Bricks are defined as stones made of clay, with or without added substances, that have been sun-dried for several days and then burned at high temperatures to harden and prevent breaking when soaked in water.[6] The brick-making process is divided into three stages: preparation of basic materials, molding, and burning.[7]

The brick-burning process can cause substantial health concerns for workers due to particle expulsion during the process.[8] Dust particles from Brick-making degrade air quality and can cause chronic obstructive pulmonary disease (COPD), asthma, bronchitis, silicosis, and other pulmonary issues. Silica exposure is one of the most vital risks linked to brick dust inhalation, as the material itself is carcinogenic.[9] Continuous exposure over an extended time can result in impaired lung function and respiratory problems among workers.[10]

Particulate matter, a major air pollutant, consists of fine particles like PM2.5 and PM10, which can penetrate deep into the respiratory system and cause severe health issues.[2,11] The size of PM determines its capacity to penetrate the respiratory tract, skin, and mucosa.[2] PM2.5 also known as fine air particles, are dust particles with a diameter of 2.5 µm produced by anthropogenic activities such as motor vehicles, biomass burning, and gasoline combustion. Brick-making processes emit the major pollutant, particulate matter with a diameter of ≤10 µm (PM10), which poses a significant health risk to workers.[12]

In 2016, it appeared that PM pollution caused around 4 million deaths (or 7.5% of all-cause mortality). A 2018 study by Guo et al found that every 5 µg/m2 increase in PM2.5 was associated with a decrease in forced vital capacity (FVC) by 1.18%, forced expiratory volume in 1 second (FEV_1) by 1.46%, and the FEV_1/FVC ratio by 0.21%. Long-term exposure to PM2.5 is linked to lung function disorders and an increased risk of COPD. This emphasizes the importance of a global effort to reduce air pollution, enhance lung health, and prevent COPD.[13]

In Indonesia, a study was conducted on red brick craftsmen in the Badung district that resulted in most craftsmen being exposed to dust exceeding the

threshold value (3 mg/m3), with an average of 9.8 mg/m3, and having impaired lung function capacity (92.86%), with the kind of impairment being mixed restrictive and obstructive.[14] Then, a study on merchants in Kampung Rambutan reveals a risk of reduced respiratory function after 30 years of exposure to PM2.5 particles.[15]

The brick industry in Aceh Besar, established in the 1980s, has expanded rapidly, raising concerns about occupational health risks due to high PM exposure and inadequate use of protective equipment. Occupational health and safety issues continue to arise, including the fact that many industrial workers do not wear personal protective equipment (PPE) like masks or nose protectors. The brick industry can emit air pollutants, including particulate matter (PM).[16,17]

Exposure to PM has been linked to decreased lung function, the appearance of respiratory complaints such as coughing and shortness of breath, as well as increased systemic inflammation and oxidative stress, but more research is needed to determine the relationship between PM and lung health in brick craftsmen.[16]

Spirometry is a physiological test that measures the ability to inhale and exhale air over time. It is commonly used as a diagnostic approach for evaluating respiratory disorders, especially to assess the risk of drug exposure in smokers and workers at the workplace. Spirometry yields three key results: FVC, FEV_1, and the FEV_1/FVC ratio.[18]

Age, medical history, working hours, smoking history, and the use of PPE at work all affect lung vital capacity. The existence of this brick industry can produce air pollutants, one of which is PM), which is very dangerous for the airways.

Therefore, this study investigates the association between PM2.5 exposure, duration of exposure, respiratory complaints, and lung function abnormalities among brick craftsmen in Aceh Besar. This research is intended to serve as a basis for future prevention efforts at work.

METHOD

This study was carried out on nine brick manufacturers in Darussalam District, Aceh Besar Regency, in September 2023. This observational, cross-sectional study was conducted in nine brick manufacturing units in Darussalam District, Aceh Besar, in September 2023. All eligible brick craftsmen (N=68) were included using a total sampling technique. This study was approved by the Health Research Ethics Committee of Zainoel Abidin Hospital and the Faculty of Medicine, Universitas Syiah Kuala (171/ETIK-RSUDZA/2023).

The study participants were brick craftsmen who did not currently or had previously suffered from lung function disorders such as pulmonary TB, COPD, and asthma, and also had no contraindications for spirometry. A questionnaire was used to determine general characteristics, length of exposure,

and respiratory complaints; lung function was evaluated using spirometry; and PM levels were quantified using an air quality monitor detector. The Spearman test and multivariate logistic regression were used to determine the causal relationship between PM and duration of exposure, respiratory symptoms, and lung function. A 95% confidence interval (CI) and α=0.05 value suggest a significant difference between variables (P≤0.05).

RESULTS

This study was conducted in nine brick factories in Aceh Besar Regency, with a total of 68 brick craftsmen as participants. Table 1 shows the overall characteristics of the research subjects.

Of the 68 participants, 58.8% were female, and 76.5% were aged 30 years or older. Most participants (67.7%) had a normal BMI, while 14.7% were overweight, and 10.3% were classified as obese. Most participants (97.1%) did not use masks while working, and 64.7% were non-smokers. PM2.5 levels were hazardous in all nine brick factories (100%). PM10 levels were hazardous in 44.4% of factories and very unhealthy in 55.6%.

Based on a lung function test among brick craftsmen, normal lung function was reported by 25 participants (36.8%), while restrictive lung type disorder affected 32 people (47.1%). The mean percentage FVC of 68 participants was 78.85, with a standard deviation of 17.03. The average FEV_1 percentage was 78.24±17.49, while the average FEV_1/FVC ratio was 84.49±16.14. Tables 2 and 3 show the frequency distributions of pulmonary function and spirometry examination results.

Table 1. Characteristics of Research Subject (N=68)

Characteristic	N	%
Sex		
Male	28	41.2
Female	40	58.8
Age		
<30 years old	16	23.5
≥30 years old	52	76.5
BMI		
Very underweight	1	1.5
Underweight	4	5.9
Normal	46	67.6
Overweight	10	14.7
Obesity	7	10.3
Using a mask while working		
Yes	2	2.9
Nos	66	97.1
Smoking		
Smoker		
Mild	9	13.2
Moderate	7	10.3
Severe	8	11.8
Non Smoker	44	64.7
Job at the brick factory		
Molding	46	67.6
Burning	22	32.4

Furthermore, the PM value was measured with an air quality monitor detector. According to Table 2, PM2.5 levels from the nine brick factories are hazardous, while four factories have PM10 levels in the hazardous category, and the rest are categorized as very unhealthy.

Table 2. PM2.5 dan PM10 Level at Brick Factories in Aceh Besar

Characteristic	N	%
PM2.5 Index		
Good	0	0.0
Moderate	0	0.0
Unhealthy	0	0.0
Very Unhealthy	0	0.0
Hazardous	9	100.0
PM10 Index		
Good	0	0.0
Moderate	0	0.0
Unhealthy	0	0.0
Very Unhealthy	5	55.6
Hazardous	4	44.4

The length of exposure was calculated using the subject's exposure time and work period in the brick-producing area, as shown in Table 3. The study indicated that 51 individuals (75%) have been working for more than three years, with 68 subjects (100%) working at least eight hours per day.

Table 3. Length of Exposure and Working Period among Brick Craftsmen in Aceh Besar

Characteristic	N	%
Length of Exposure		
<8 hours/day	0	0.0
≥8 hours/day	68	100.0
Work Period		
<1 years	2	2.9
1-3 years	15	22.1
>3 years	51	75.0

Brick craftsmen's respiratory issues were evaluated based on the presence of cough, shortness of breath, sputum production, or chest pain. Coughing was the most common symptom (23.5%) among brick craftsmen, followed by shortness of breath (13.2%) and chest pain (2.9%).

Furthermore, bivariate analysis was carried out to assess the association between PM10 and PM2.5 with lung function disorder, as indicated in Table 4. The correlation test revealed a significant association between either $PM_{2.5}$ or PM10 and lung function impairments (values of P=0.002 and 0.012, respectively).

The correlation coefficient indicates a negative association between variables, implying that the higher the amounts of PM, the lower the lung function. In addition, a correlation test was performed between the work period and respiratory complaints as well as lung function disorder.

The investigation revealed that there was no link between work periods and respiratory complaints among brick craftsmen in Aceh Besar (P=0.107). The work period and lung function abnormalities had a significant association (P=0.037); the longer the patient worked, the more impaired the lung function. In this study, a multivariate logistic regression test was performed and found that there was no correlation between PM, work period, or respiratory problems among the study participants.

A multivariate analysis between particulate matter, work period, and lung function abnormalities revealed that a working period of 1-3 years was significantly associated with lung function abnormalities (FEV_1) in brick craftsmen in Aceh Besar (P=0.026).

Table 4. The Relationship between PM2.5 and PM10 with Lung Function Disorder among Brick Craftsmen in Aceh Besar

	FVC (ml)	FEV_1 (ml)	FEV_1/FVC
PM2.5			
Correlation Coefficient (r)	0.162	-0.167	-0.367
P	0.188	0.174	0.002
PM10			
Correlation Coefficient (r)	0.118	-0.145	-0.304
P	0.336	0.237	0.012

Table 5.The result of Multivariate analysis between Particulate Matter, Work Period, and Lung Function among Brick Craftsmen in Aceh Besar

Variable	Regression Coefficient (B)		P	
	FVC	FEV_1	FVC	FEV_1
PM2.5	0.051	-0.012	0.179	0.756
PM10	-0.023	-0.004	0.394	0.876
Work period <1 years	19.748	-1.294	0.110	0.917
Work period 1-3 years	5.056	11.654	0.318	0.026

However, PM2.5, PM10, and working periods <1 year were not significantly associated with lung function abnormalities.

DISCUSSION

The brick factory emits air pollutants, such as particulate matter (PM). Exposure to PM among Brick Craftsmen has been linked to respiratory problems and reduced lung function. Workers and industry owners are unaware of the importance of personal protective equipment (PPE). The emergence of lung abnormalities is also influenced by the length of exposure and working time. Workers are more likely to acquire occupational lung disease if they are exposed often and for a long period.

In this study, the majority of the 68 participants were female (58.8%). This conclusion contrasts with Emilia's study in Central Aceh Regency, which indicated that 86.7% of participants were male.[19] Dewi's research in Semarang found that brick manufacturers were more likely to be men (53.3%).[20]

According to the study, the gender frequency distribution varies because female workers are needed for brick shaping and men for brick burning. Because of variations in lung vital capacity, this gender distribution can influence lung function analysis results. Women have about 20–25% less lung vital capacity than men. Adult men have an average vital lung capacity of 4.8 L, while women have an average of 3.1 L.

Based on age characteristics, 76.5% of study participants were 30 years or older. This is consistent with Novianto's findings in Semarang and Pramesti in Badung, where the majority of brick craftsmen are above 30.[14,21] Aging is connected with a decline in the structure and physiology of human organs, which can lead to a reduction in lung function.[21]

The majority of research participants had a normal nutritional state (67.6%). These findings are supported by Pramesti's Badung investigation, which discovered that 59.52% of respondents had a healthy nutritional status.[14] Nutritional status influences a person's lung capacity; appropriate nutritional status promotes immunity, allowing the body to protect itself against hazardous exposures that reduce lung vital capacity. Novianto found a significant link between dietary status and lung function among brick workers in Semarang.[21]

Almost all study participants (97.1%) did not utilize masks as PPE, which is extremely harmful to workers because it can cause respiratory problems. These findings are consistent with a study by Yulianto et al in Pekanbaru, which discovered that 82.9% of respondents did not use masks while working in a brick production.[22]

Emilia discovered similar results, with 76.7% of brick craftsmen not using PPE while working.[19] The poor use of masks in this study could be attributed to a variety of variables, including workers' and brick factory owners' lack of awareness about the significance of utilizing PPE while working.

Personal protective equipment is a tool that workers can employ to protect part or all of their bodies from potential workplace hazards or accidents. PPE cannot eliminate potential workplace hazards or accidents; nevertheless, it can lessen or prevent the severity of occupational diseases. Special PPE for breathing protection can take the form of masks that guard against bigger dust or particles that enter the respiratory tract.[21]

Based on smoking behavior, 64.7% of respondents claimed not to smoke. These findings are consistent with Dewi's research in Penggaron Kidul, which found that the majority of study participants (66.7%) did not smoke.[20] However, research conducted by Nazira found that 64.8% of brick workers smoked.[23]

This disparity in outcomes is because women dominated the research subjects, whereas smokers are commonly seen in men. Smoking can impair lung function because the hazardous chemicals in cigarettes are poisonous to bodily tissues. Toxins in the blood hinder the exchange of O_2 gas with CO_2 in the alveoli. If cigarette exposure continues for an extended time, the alveolus will be destroyed, causing lung function to decline. Cigarette smoke increases mucus secretion, while nicotine paralyzes the cilia in the respiratory tract, affecting airway clearance.[21]

In this study, the study participant worked primarily in the brick molding section rather than the brick burning. The burning procedure is not done every day and is only for males, but brick molding requires a larger workforce, which is dominated by women.

Spirometry results suggest that the majority of lung function disorders are restrictive types, followed by obstruction and mixed types (obstruction and restriction). These findings are consistent with Dewi's research, which revealed that

20% of brick craftsmen suffered from restriction lung disorder.[20]

There are two types of ventilation abnormalities: restriction and obstruction disorders. Restriction is defined as the halting of lung growth due to any cause. In restriction disorders, the lung becomes rigid, increasing the inward pull and shrinking the chest wall. This reduces lung volume and narrows the rib cage. Restriction disorders are identified by spirometry data when the FVC is less than 80% of the anticipated value. Obstruction disorders cause a decrease in expiratory flow velocity and normal vital capacity. Because airflow is increased, essential capacity may decrease due to trapped air. This lung condition is identified by spirometry readings of FEV_1/FVC <75%.[24]

Measurements of particulate matter revealed that PM2.5 levels in the nine brick manufacturers were in the hazardous category, as were PM10 levels in four factories, but the other five factories have PM10 levels in the very unhealthy category. Dewi et al found that dust levels in all brick-making locations in the Tenayan Raya Sub-district exceeded the established threshold value, with an average PM10 of 471.28 $\mu g/Nm^3$.[25]

Rohmawati's investigation in Kaloran Village yielded similar results, with PM2.5 levels at the brick factory exceeding the threshold. Dust levels beyond the threshold can induce respiratory issues, eye irritation, allergies, and impaired lung function in workers.[26] The majority of individuals (75%) have worked for more than three years and work a minimum of eight hours every day. This survey is consistent with research undertaken by Nazira in Talang Belido village, which found that 71.1% of respondents had worked for more than five years.[23]

Siregar's investigation in Deli Serdang revealed that the majority of workers were exposed to dust for more than eight hours every day.[27] The longer the worker works, the more dust settles in their lungs. The effect of dust exposure is determined by the dose or concentration, as well as the location and timing of exposure.[21]

The most common respiratory problems in this study were coughing (23.5%) and shortness of breath (13.2%). These findings are consistent with Siregar's research, which found that 76.5% of brick-making workers reported coughing and shortness of breath while at work.[27]

Ridayanti's study of people living near brickmaking factories found that 25.1% had shortness of breath, 30.6% frequently coughed, 35% had eye discomfort, and 9.2% had allergies. Exposure to PM2.5 produces coughing as a defensive mechanism to eliminate foreign bodies from the body. If this exposure persists, it can lead to ventilation problems and decreased lung function.[28]

The findings revealed a strong link between PM2.5 and PM10 levels and pulmonary function impairments in brick craftsmen in Aceh Besar. Harmanto's study, which discovered a link between exposure and lung function capacity in brick-burning workers in Karanganyar, supports these findings.[29]

According to Pramesti's research, workers who are exposed to dust that exceeds the threshold (>3 mg/m^3) are 1.45 times more likely to have decreased lung function capacity than those who are exposed to dust that is below the threshold.[14] Mengkidi discovered contradicting results on employees of PT Semen Tonasa-Pangkep in 2006, indicating that dust levels and lung function abnormalities had no significant link.[30]

The correlation test revealed that there was no association between length of exposure and respiratory complaints among brick craftsmen in Aceh Besar. This finding is consistent with Dewi's study, which found no link between length of exposure (work period) and respiratory problems. Siregar found that long exposure to dust in Brick-making workers was connected with the development of respiratory complaints (cough, shortness of breath, nasal congestion, and throat pain).[27]

This disparity in results could be attributed to a variety of factors, including the fact that the study participants are dominated by female workers who work long hours, brick burning is not done by women, the brick-burning site is located far from the brick molding site, and no female workers who smoke.

In this study, the length of exposure was linked to lung function impairments determined by spirometry results. The findings of this study are consistent with prior research conducted by Novianto and Dewi in Semarang, where the work period is substantially associated with reduced pulmonary function among brick craftsmen.[20,21] The longer someone works, the more harmful compounds they are exposed to in the workplace that can impact and impair employees' lung function capacity.

A multivariate analysis revealed that PM and work period were not substantially associated with respiratory complaints. This finding is consistent with Dewi's research, which demonstrated no link between dust exposure and working hours with respiratory symptoms.[25] This condition can emerge because respiratory complaints are impacted by a variety of circumstances, including smoking habits, a history of respiratory disease, the use of PPE, etc.[31] Furthermore, the demographic features of the respondents, who were overwhelmingly female, influenced the study's findings.

The multivariate test findings for lung function disorder (measured by FEV_1) showed that they were only connected with 1-3 years of employment, but not with dust exposure or <1 year of work duration. The longer workers are exposed to dust, the higher the risk of lung function problems, as indicated by this study's result that a working period of 1-3 years is related to lung function disorders. Based on these findings, it is possible to assume that working with dust exposure that exceeds the threshold over an extended time will impair lung function.

This study found no significant limitations that could affect the validity or reliability of the findings.

CONCLUSION

This study showed that Particulate Matter was associated with impaired lung function, although there was no significant association with respiratory complaints. Furthermore, a long working period is significantly associated with respiratory symptoms, especially for workers with 1-3 years, and is associated with impaired lung function in brick artisans in Aceh Besar. Since brick kilns generate pollutants, restricting kiln emissions and continuously implementing preventive measures while working is essential.

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Case Report

Physical Medicine and Rehabilitation Management in Patients with Long COVID-19 and Thymoma-associated Myasthenia Gravis: A Case Report

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Submitted: August 21st, 2024
Accepted: October 14th, 2024
Published: October 31st, 2024

Respir Sci. 2024; 5(1): 40-7
https://doi.org/10.36497/respirsci.v5i1.156

Abstract

Background: Myasthenia gravis is an autoimmune disease that causes muscle weakness and fatigue due to antibodies attacking the acetylcholine receptor. In patients with MG, fatigue can be worsened by concurrent long COVID, leading to further deterioration of cardiorespiratory function.

Case: A 44-year-old woman with long COVID syndrome and thymoma-associated myasthenia was given an exercise program that aimed to overcome fatigue so that the patient could carry out her role as a housewife, and to prepare for thymectomy surgery. Before exercise, patients were educated to take pyridostigmine 1 hour earlier. During exercise, the patient was monitored to prevent excessive fatigue. At the end of the training session, the patient was asked to observe for signs of exacerbation until the next training session.

Discussion: Pulmonary rehabilitation (PR) can be beneficial for patients with thymoma-associated MG and long COVID-19, but it requires special strategies. PR typically starts with light weights and gradually increases in intensity. It has been shown to improve fatigue and cardiorespiratory endurance, as indicated by a successful 6-minute walk test after 4 weeks of training intervention.

Conclusion: Pulmonary rehabilitation plays an important role in increasing cardiorespiratory endurance and functional capacity for surgery preparation. The provision of pulmonary rehabilitation programs must be tailor-made according to the patient's functional ability and underlying disease to achieve optimal goals.

Keywords: long COVID-19, myasthenia gravis, thymoma

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder in which the body's immune system attacks the acetylcholine receptor (AChR), a protein that helps nerves send signals to muscles. This can decrease muscular endurance and respiratory complications. A thymoma is a

tumor of the thymus gland that is associated with MG. About 10-20% of people with MG have thymoma, and about 30% of people with thymoma have a secondary MG. The first line of treatment for thymoma has been recommended to be thymectomy.[1,2]

Presently, there is no evidence to support a connection between COVID-19 infection and the onset of MG. Due to several circumstances, including decreased baseline respiratory efficiency and the immunocompromised state brought on by immunosuppressive therapy, patients with MG are more likely to contract severe COVID-19. The use of immunosuppressive corticosteroids is associated with an increased risk of infection, up to 50%.[3]

The subacute and long-term consequences of COVID-19, which can influence numerous organ systems, are being studied by clinical evidence and science. According to early reports, SARS-CoV-2 infection may still cause symptoms like fatigue, chest pain, dyspnea, cognitive problems, and a deterioration in quality of life.[4]

Pulmonary rehabilitation can help improve physical function, endurance, performance, and participation in work and social activities for people with lung diseases.[5] In this case report, we will describe the role of pulmonary rehabilitation in patients with long COVID syndrome and thymoma-associated myasthenia gravis and preparation for thymectomy surgery.

CASE

A 44-year-old female patient was consulted to the rehabilitation department in preparation for surgery with dyspnea on effort caused by long COVID-19 syndrome and thymoma-associated MG in early 2022. She complained of shortness of breath, especially when speaking, coughing, doing household activities, and ambulating inside the house.

The patient was diagnosed with a thymoma in 2012 and has not been operated on. In 2015, she was also diagnosed with MG and received pyridostigmine 240 mg/day, methylprednisolone, and azathioprine. In 2017, the patient experienced shortness of breath again and was treated at the hospital with plasmapheresis 5 times, and the pyridostigmine dose was increased. Afterward, the patient experienced no symptoms of shortness of breath or weakness.

In 2021, the patient was hospitalized once more due to complaints of shortness of breath, weakness, especially the eyelids that were difficult to open and close in the afternoon, coughing with phlegm, and painful swallowing. The results of the PCR COVID-19 test were positive. She was treated in the intensive care unit and supplemented with oxygen using a high-flow nasal cannula at 21 lpm and FiO_2 of 70%. At that time the patient was diagnosed with moderate acute respiratory distress syndrome due to COVID-19 and myasthenia gravis.

After treatment, the patient was still on oxygen supplementation and succeeded in not using oxygen 9 months later. In 2022, the patient was exposed to COVID once again, hospitalized, and still used oxygen only when needed after returning home.

In the Department of Medical Rehabilitation, the patient received supplemental oxygen through a nasal cannula after returning from the bathroom, as she had up to 86% oxygen desaturation. She underwent pulmonary rehabilitation in the form of aerobic exercise using an ergo cycle accompanied by oxygen supplementation and breathing exercises twice a week, for a total of 6 times.

After the patient had carried out 1 series of pulmonary rehabilitation, she came for an evaluation, and currently, complaints of fatigue have been much reduced. However, the shortness of breath still existed when she was doing daily activities. She was able to carry out daily activities independently, walking for about 10-15 minutes, and was less likely to use oxygen supplementation, but for household activities, she still often felt tired.

On physical examination, vital signs were within normal limits with oxygen saturation of 99% in room air, the BORG scale was 6–0–0, the BMI was 27.05 kg/m^2, and the fatigue severity scale decreased from 62 to 51. Chest expansion enlarged from previous 2–3–4 cm to 3–3.5–4 cm. On auscultation, bilateral pulmonary vesicular breath sounds were obtained while rhonchi, wheezing, and phlegm were absent.

In the single breath count test, 17 results were achieved whereas previously it was only 7. Sit-to-stand test for 30 seconds: the patient could do it 9 times, which was still the same as the previous examination. The 6-minute walk test result was 255 meters with a predicted VO_2 max of 12.4 ml/kg/min and converted to METs of 3.54 METs.

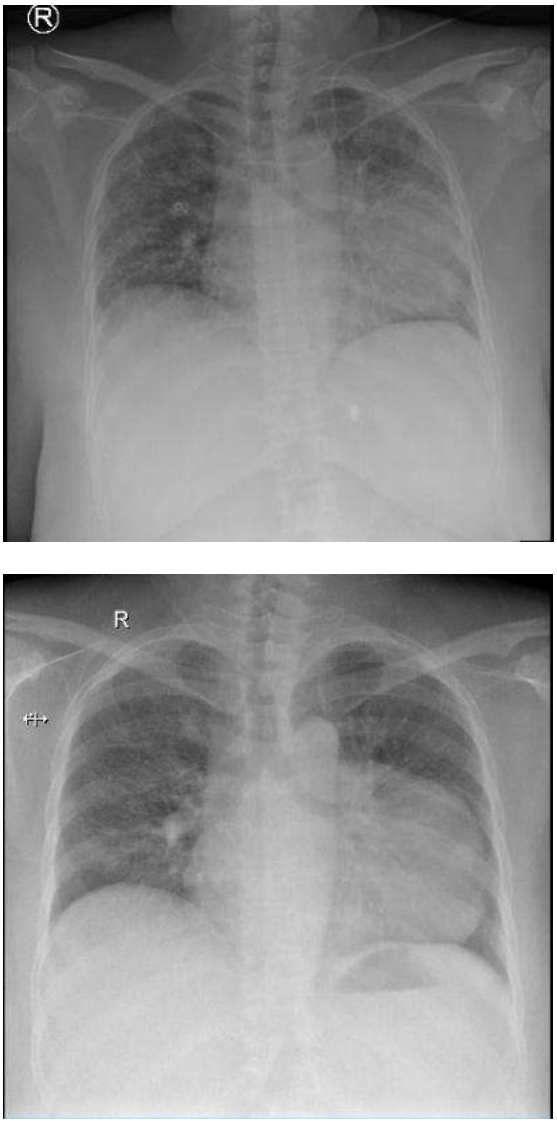

Figure 1. Chest radiograph 2021 (top) and 2022 (bottom)

On chest x-ray (CXR) examination (Figure 1), pneumonia was found in both

lungs, in conjunction with left mediastinal mass, aortic elongation and calcification. The CT scan of the thorax revealed diffuse ground glass opacity and thickening of the interlobular septa in almost all segments of both lungs with suspected pneumonia, a left anterior mediastinal mass attached to the pleura and pericardium, and a mass in the supraclavicular to the superior mediastinum, relatively the same size, multiple.

DISCUSSION

A neuromuscular junction autoimmune illness called myasthenia gravis is clinically characterized by the weakening and fatigue of several skeletal muscles. Antibodies that directly affect the neuromuscular junction are the clinical hallmark of striated muscle weakness. Muscular weakness in MG can influence the ocular, limb, respiratory, and bulbar muscles; it can change over time and is frequently brought on by exertion.[6,7]

Due to the risk of overloading weakened muscles, physicians who treat patients with neuromuscular disorders have typically been reluctant to actively encourage physical activity. Modern immunosuppressive, symptomatic, and supportive treatments have advanced to the point where most well-controlled MG patients now have a positive outlook, a normal life expectancy, and minimal impact on daily activities.[6,7]

The evaluation of physical activity in MG presents certain difficulties in measuring fatigue objectively. Exercise triggers an immunological response that results in an increase in T regulatory cells, a decrease in immunoglobulin secretion, and a change in the Th1/Th2 balance that favors decreasing the production of Th1 cells.[6]

Exercise can be challenging for people with MG due to proximal muscle weakness, fatigue, and respiratory muscle dysfunction.[6] The prevalence of fatigue in MG is similar to that of other neuromuscular disorders, with rates between 61–74% in facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy, and hereditary motor and sensory neuropathy type 1.[3] Fatigue in MG patients can be caused by several factors, including female gender, the presence of both anticholinergic receptor and muscle-specific receptor tyrosine kinase (MuSK) antibodies, and higher depression rates.[7]

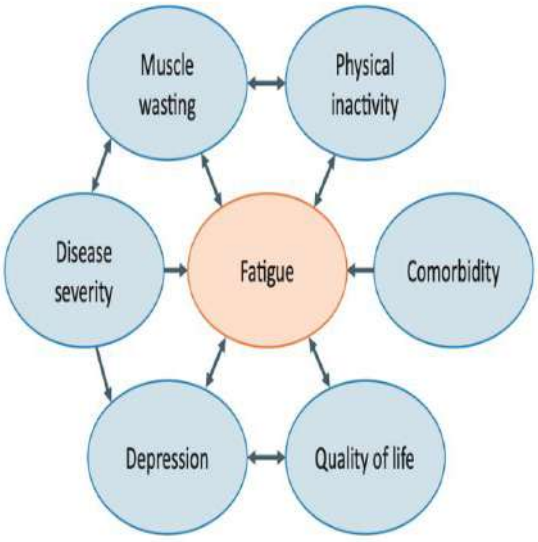

Figure 2. Model illustrating how fatigue is multifaceted[7]

It has been theorized, based on some studies, that muscular damage causes fatigue (Figure 2) via a central nervous

system-driven process to momentarily down-regulate physical activities and keep muscles from injury. In patients with neuromuscular diseases, chronically low levels of physical activity likely have a deleterious impact on muscle mass and strength, creating a vicious cycle. Obesity can result from a lack of physical activity. A significant proportion of MG patients are overweight (BMI ≥ 25) as a result of their combination of prolonged steroid treatment and inactivity.[7]

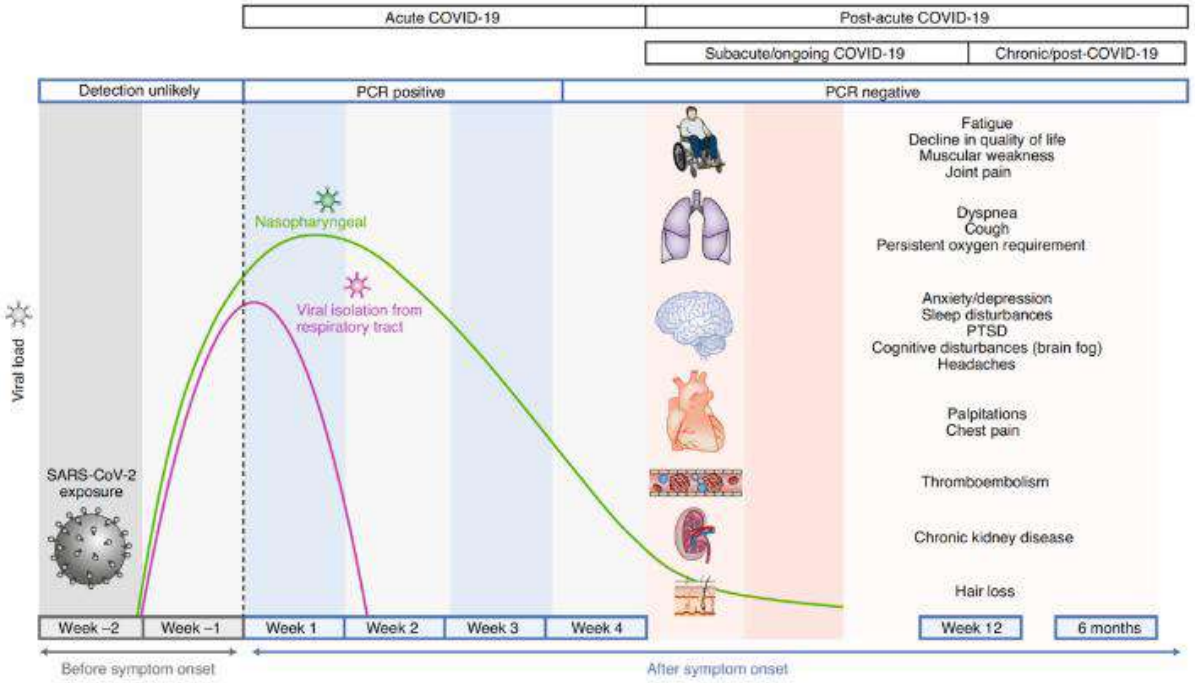

Figure 3. Timeline of post-acute COVID-19[4]

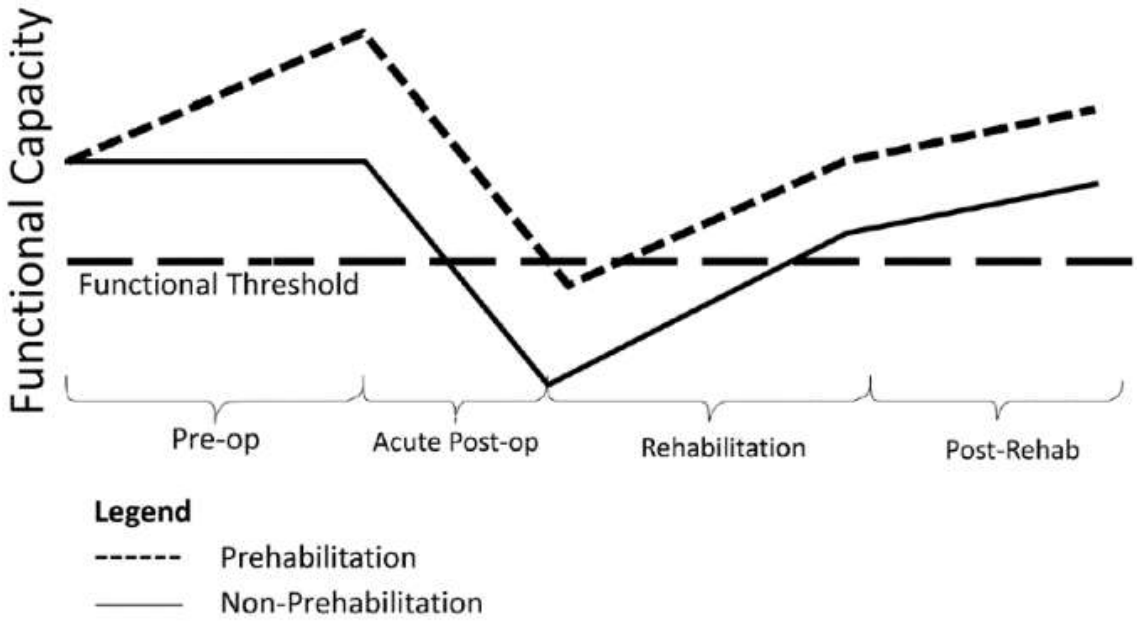

Figure 4. Conceptual model of generalized functional ability progression in patients receiving prehabilitation vs. simply rehabilitation prescriptions[8]

Post-acute COVID-19 is a condition that can occur after a SARS-CoV-2 infection. It is characterized by persistent symptoms and/or delayed or long-term complications that develop more than 4 weeks after the onset of symptoms.[4]

Figure 3 illustrates the timeline of post-acute COVID-19 into two categories: subacute or ongoing symptomatic COVID-19, which is characterized by symptoms and abnormalities that are present from 4 to 12 weeks after the onset of acute COVID-19, and chronic or post-COVID-19 syndrome, which is characterized by symptoms and abnormalities that persist or are present more than 12 weeks after the onset of acute COVID-19, and are not caused by other conditions.[4] This is what caused the patient's fatigue to worsen, especially post-COVID-19.

Numerous physical conditions can be treated with surgery, but this major stressor frequently has negative impacts on a patient's ability to carry out daily activities and decreases the quality of life. Prehabilitation is a method of preparing surgery candidates using multiple techniques (Figure 4) intended to enhance their physical, physiological, metabolic, and psychosocial reserves.[8]

Prehabilitation is the process of improving physical and mental health to protect against the potentially harmful effects of surgery. It involves preoperative physical and psychological conditioning to build up bodily and mental fitness and prevent the anticipated functional and well-being declines associated with surgery.[8]

Patients receive treatment on an outpatient basis. Pulmonary rehabilitation is provided in the form of breathing control exercises, chest expansion exercises, aerobic exercises, and strengthening exercises. Before training, patients were given education to consume pyridostigmine. The peak effect of pyridostigmine is about 30 to 60 minutes after consumption. During exercise, the patient is still asked to do breathing control so that the lungs continue to work efficiently.

Exercises are given slightly differently from the patient in general. Patients with MG and long COVID syndrome tend to get tired quickly, so the dose of exercise, especially resistance training, starts with light weights and then progressively increases. After the exercise, the patient was asked to evaluate whether there were symptoms of exacerbation of MG.

Rehabilitation plays an important role in the management of post-COVID-19 syndrome. Studies pointed out that endurance, strength, inspiratory muscle training, expectorant training, and diaphragm training exhibited improvement from baseline.[9–11] Rehabilitation programs should be personalized, safe, and supportive to sustain function without symptom exacerbation.[12]

Other studies concluded that cardiopulmonary rehabilitation consisted of aerobic exercise, muscle strengthening, and respiratory exercise 3 times per week over 8 weeks indicated improvement.[13] However, early rehabilitation is vital for the long-term recovery and functional

improvements of post-COVID-19 syndrome patients.[14,15]

CONCLUSION

The pulmonary rehabilitation program is effective in increasing cardiorespiratory endurance, and it plays an important role in preparing patients for surgery to increase their functional and mental capacity when dealing with physiological stressors from surgery and anesthesia. After the rehabilitation program, the patient shows improvement in shortness of breath, fatigue severity scale, chest expansion, single breath count test, and the 6-minute walking test. Pulmonary rehabilitation programs must be tailor-made according to the patient's functional ability and underlying disease to achieve optimal goals.

ACKNOWLEDGMENTS

The authors would pay gratitude to all authors, professors, experts, assistants, and public cadres, and also to the Cardiorespiratory Division, Department of Physical Medicine and Rehabilitation, Universitas Indonesia Hospital, and Departments of Physical Medicine and Rehabilitation Universitas Indonesia, Cipto Mangunkusumo Hospital.

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Literature Review

Obesity Hypoventilation Syndrome (Pickwickian Syndrome): A Literature Review

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Submitted: August 20th, 2024
Accepted: November 7th, 2024
Published: November 29th, 2024

Respir Sci. 2024; 5(1): 48-61
https://doi.org/10.36497/respirsci.v5i1.155

Abstract

Obesity hypoventilation syndrome (OHS), also known as Pickwickian syndrome, is a respiratory disorder characterized by reduced alveolar ventilation and elevated daytime carbon dioxide levels, primarily associated with obesity. If untreated, OHS can progress to pulmonary hypertension (PH) and ultimately heart failure. The exact prevalence of OHS in the general population remains unclear, but studies estimate it to range from 8% to 12.3%, increasing with obesity prevalence. This review discusses the diagnostic criteria for OHS, the utility of the STOP-Bang questionnaire in screening, and advances in understanding the pathophysiology and management of OHS, focusing on heart failure with preserved ejection fraction (HFpEF). Accurate diagnosis of OHS is critical and requires a thorough approach involving an extensive patient medical history and physical examination to differentiate OHS from obstructive sleep apnea (OSA). Key diagnostic tests include serum bicarbonate levels and arterial blood gas (ABG) analysis, to confirm the hypercapnia and identify the severity of hypoventilation. Given the rising prevalence of obesity worldwide and the serious complications associated with untreated OHS, early and accurate identification of OHS is essential, as it can prevent the progression to severe pulmonary hypertension (PH) and the subsequent development of heart failure (HF).

Keywords: HFpEF, obesity hypoventilation syndrome, Pickwickian syndrome

INTRODUCTION

Obesity hypoventilation syndrome (OHS), also known as Pickwickian syndrome, is characterized by obesity (BMI ≥30 kg/m²) and chronic daytime hypoventilation with hypercapnia ($PaCO_2$ >45 mmHg), in the absence of significant underlying pulmonary, metabolic, or neuromuscular disorders.[1]

In patients with OHS, OSA frequently coexists as a concurrent condition. As a result, the majority of prevalence studies have concentrated on individuals referred to sleep centers for the assessment of sleep-related breathing disorders, leading

to a reasonable estimate of OHS prevalence among OSA patients.[2] Numerous studies have found that the prevalence of OHS ranges between 8-12.3%.[3,4] OHS is strongly associated with cardiometabolic comorbidities, including pulmonary hypertension (PH), heart failure (HF), and coronary artery disease.[1]

The five-year mortality rate was 15.5% in the OHS group, compared to 4.5% in the OSA group. It has been reported that patients with OHS experienced a two-fold increased risk of mortality and are 1.86 times greater risk of experiencing a cardiovascular event.[5]

Given these outcomes, it is crucial for clinicians to properly identify and manage OHS, however, the condition is often neglected.[2] Therefore, This review examines the pathophysiology, diagnostic criteria, screening methods, and management strategies for OHS, with a particular focus on its role in heart failure with preserved ejection fraction (HFpEF).

RESPIRATORY PHYSIOLOGY

Normally, gas moves from high-pressure to low-pressure areas based on Boyle's principle. During respiration, inspiration and expiration involve the coordinated action of the diaphragm and rib muscles, working together to contract and relax, changing the volume of the lungs and creating a pressure gradient that allows airflow into and out of the lungs.[6]

The lungs are elastic structures that rely on the proper stretching of elastic fibers to function. Lung collapse is prevented by the pleura, comprising the parietal and visceral layers, which maintain lung integrity through cohesive forces.[7]

Intrapleural pressure at rest is approximately -4 mmHg relative to atmospheric pressure and decreases to around -18 mmHg during maximal inspiration, ensuring lung expansion.[7] Additionally, the pleural liquid acts as a lubricant during ventilation, providing cohesive force between the pleural layers. These mechanisms maintain the elasticity of the lungs.[8]

RESPIRATORY FAILURE

Respiratory failure occurs when the pulmonary system fails to adequately exchange gases, defined by a partial pressure of oxygen (PaO_2) <60 mmHg and/or partial pressure of carbon dioxide ($PaCO_2$) >50 mmHg.[9]

Respiratory failure can result from central or peripheral nervous system dysfunction, airway obstruction, or alveolar disorders. It is categorized by onset (acute, chronic, or acute-on-chronic) and by arterial blood gas (ABG) abnormalities as type 1 (hypoxemic) or type 2 (hypercapnic).[9]

Type 1 respiratory failure, or hypoxemia, is characterized by a PaO_2 <60mmHg with or without changes in $PaCO_2$. Alveolar disorders, including pulmonary edema and pneumonia, commonly cause this condition. Type 2 respiratory failure, or hypercapnia, is characterized by an increase in $PaCO_2$ >50mmHg, which is often accompanied by

hypoxemia. This condition is typically caused by airway obstruction or neuromuscular disorders.[9]

Acute respiratory distress syndrome (ARDS) results in respiratory failure and occurs in individuals with pneumonia, sepsis, gastric acid aspiration, or trauma. ARDS is marked by hypoxemia, lung edema, and the requirement for a ventilator. It causes damage to the alveolar epithelium and lung tissue.[10]

Conditions that cause type 1 respiratory failure include decreased inspiratory PaO_2, alveolar hypoventilation, ventilation/perfusion (V/Q) inconsistency, diffusion defect, and shunt from right to left. Decreased inspiratory PaO_2 occurs when the fraction of inhaled oxygen (FiO_2) is reduced, which occurs at high altitudes where barometric pressure is lower.[11]

Diffusion disorders occur when gas exchange is disrupted due to damage to the alveolar or blood vessel walls, as seen in pulmonary edema, pulmonary fibrosis, and ARDS. V/Q mismatches occur when ventilation decreases in areas with normal perfusion or when ventilation is normal in areas with decreased perfusion, such as pulmonary embolism, airway obstruction, and pneumonia. Right-to-left shunt occurs when oxygenated blood mixes with deoxygenated blood.[11]

Type 2 respiratory failure can be triggered by factors such as reduced alveolar ventilation due to airway obstruction, decreased respiratory function in neuromuscular diseases, and damage to the brain and spinal cord, decreasing the respiratory drive. Additionally, increased CO_2 production can occur in conditions that boost metabolism, such as sepsis, fever, or burns.[11]

OBESITY HYPOVENTILATION SYNDROME

Definition

OHS is defined as the coexistence of obesity, persistent alveolar hypoventilation ($PaCO_2$ ≥45 mmHg), and daytime hypoxemia (PaO_2 <70 mmHg), often accompanied by sleep-related respiratory disorders.[12]

Pathophysiology

The mechanisms underlying obesity-induced hypoventilation are complex and not fully understood. Hypothesized mechanisms include altered respiratory mechanics due to excess weight, impaired central responses to hypercapnia and hypoxemia, the presence of sleep-disordered breathing, and leptin resistance.[13]

Obesity results in significant mechanical stresses, reducing total respiratory compliance, increasing pulmonary resistance, and weakening the respiratory muscles, which encourages impaired respiratory function.[13]

Obese patients often enhance their respiratory function to keep CO_2 levels normal. Nevertheless, changes in their breathing effort can cause hypoventilation, particularly during paradoxical sleep. In this phase, muscle relaxation occurs, and the ventilation is controlled by the diaphragm and central nervous system. This leads to a suppression of respiratory

centers, causing daytime hypercapnia. This may explain the high occurrence of central hypoventilation in the OHS.[12]

A pathophysiological model of OHS has been suggested that integrates sleep-related respiratory disorders, central respiratory drive, and renal compensation. In OSA patients, there is stable minute ventilation during sleep due to a marked rise in minute ventilation between episodes of obstructive apnea. Nevertheless, OSA can result in acute hypercapnia if the periods of hyperventilation between apneic events are insufficient to clear the built-up CO_2.[12,14]

The present condition results in a modest elevation in serum bicarbonate levels that remain uncorrected before the subsequent sleep period, as the CO_2 excretion time is shorter than bicarbonate. An increase in serum bicarbonate concentration diminishes the baseline ventilatory response to CO_2 by decreasing the shift in hydrogen ion concentration for a specific increase in CO_2. Consequently, this leads to elevated CO_2 levels during wakefulness. [12,14]

Risk Factors

Key risk factors for OHS include severe obesity (BMI >40 kg/m²), OSA with an apnea-hypopnea index (AHI) >50 events/hour, oxygen saturation below 60% during polysomnography, moderate-to-severe lung function limitations, and large neck, waist, and hip circumferences.[15]

Clinical Manifestations and Diagnosis

Most cases are diagnosed when the patient seeks medical attention in an acute condition, such as severe acute exacerbations characterized by acute respiratory acidosis or sleep disorders. The onset of OHS can vary, but it typically appears in the age range from 50 to 60. Its presentation is often diverse, with a wide range of clinical severity.[16]

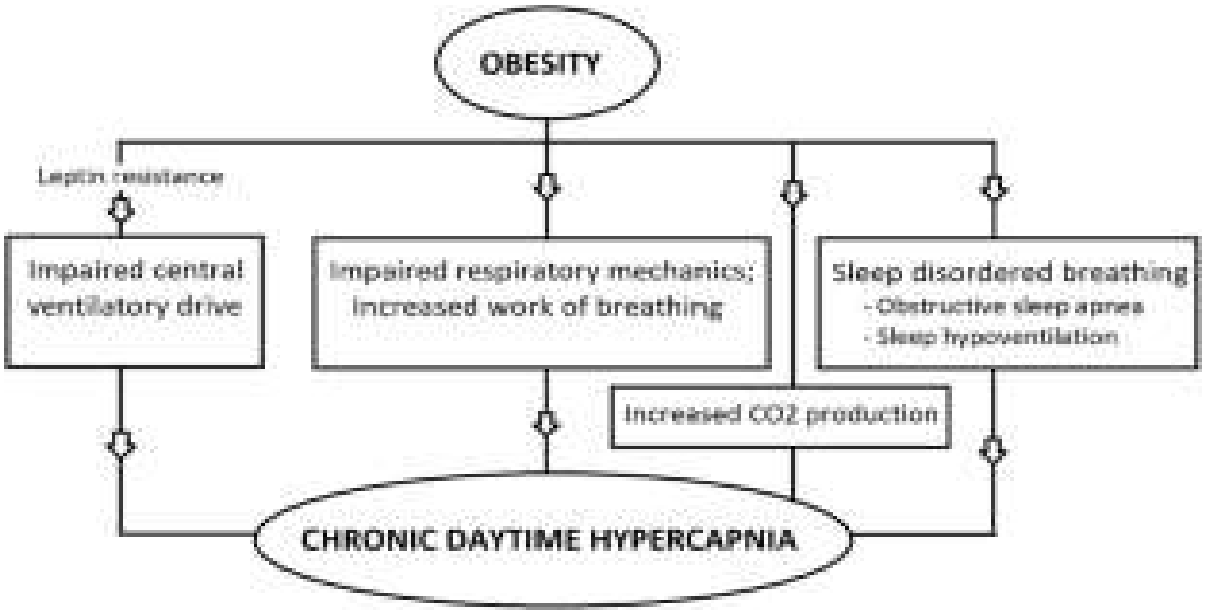

Figure 1. OHS Pathophysiology[14]

Symptoms arise from obesity and disrupted sleep, including fatigue, persistent daytime sleepiness, morning headaches, mood disturbances, difficulty concentrating, and memory impairment.[16]

The signs and symptoms in patients with OSA are heavy snoring with a crescendo-decrescendo pattern, nighttime choking, and gagging, as well as apneas observed by the bedmate.[16] Physical exam shows a typical obese person, who has a short and broad neck, a congested oropharynx, and a low-hanging uvula. They often showed signs of right HF due to PH, such as elevated JVP, an accentuated pulmonic component of the second heart sound, hepatomegaly, and lower extremity edema.[17]

Hematological examination reveals polycythemia with a hematocrit of over 50% and erythrocytosis. A room air ABG analysis remained the gold standard for diagnosing hypoventilation, which shows a reduction in PaO_2 and a rise in $PaCO_2$ during sleep and awake hours. Chronic hypercapnia in OHS patients will show elevated serum bicarbonate levels (>27 mEq/L) resulting from metabolic adjustment to chronic respiratory acidosis.[16]

A new noninvasive method for monitoring hypercapnia during the night and day is end-tidal or transcutaneous CO_2 monitoring. Lung function assessment including lung volume and capacity measurements, and spirometry where applicable, along with flow-volume loops and indices to check any obstruction in the upper airway.[16]

Additionally, hypercapnia should be considered if hypoxemia is detected on pulse oximetry in a conscious patient, as hypoxemia during wakefulness is uncommon in OSA. Performing lung function tests and chest X-rays should be done to exclude other causes of hypercapnia.[1]

STOP-Bang Scoring Model	
1. Snoring Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	Yes/No
2. Tired Do you often feel tired, fatigued, or sleepy during daytime?	Yes/No
3. Observed Has anyone observed you stop breathing during your sleep?	Yes/No
4. Blood pressure Do you have or are you being treated for high blood pressure?	Yes/No
5. BMI BMI more than 35 kg/m^2?	Yes/No
6. Age Age over 50 years old?	Yes/No
7. Neck circumference Neck circumference greater than 40 cm?	Yes/No
8. Gender Gender male?	Yes/No
High risk of OSA: answering yes to three or more items Low risk of OSA: answering yes to less than three items	

Figure 2. STOP-Bang Questionnaire[18]

Nocturnal polysomnography (PSG) is used to diagnose OSA or OHS. However, the diagnosis can often be overlooked if only nocturnal pulse oximetry is used to assess sleep disorder breathing.[16]

The STOP-Bang questionnaire, commonly used for OSA, can serve as an early screening tool for OHS. It comprises 8 queries related to snoring, daytime drowsiness, noted episodes of apnea, history of hypertension, BMI, age >50, neck circumference, and gender.[18]

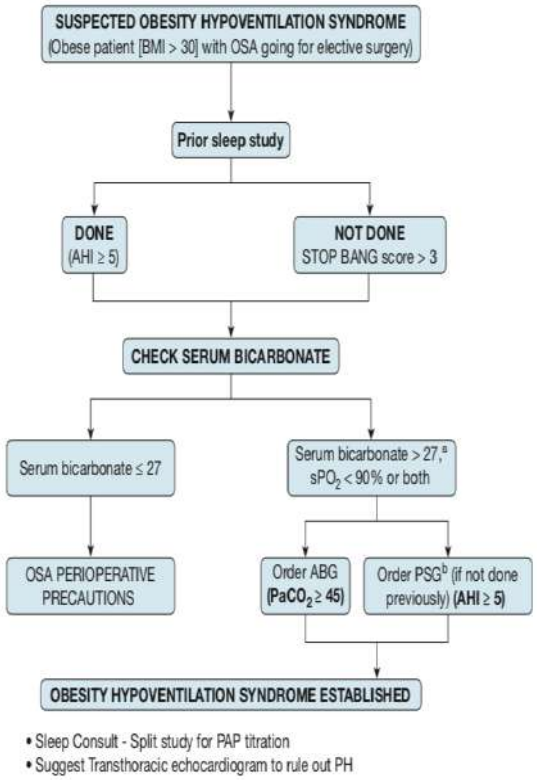

Figure 3. OHS Screening and Diagnosis Algorithm[19]

Early screening for OHS can be performed using the STOP-Bang questionnaire, assessment of oxygen saturation with a pulse oximeter, and serum bicarbonate. If the STOP-Bang score is ≥3, the SpO_2 value is <90% and the serum bicarbonate level is elevated, these findings indicate a high risk of OHS, and ABG analysis should be performed to assess for hypercapnia.[19]

HFpEF

HF is a complex medical condition characterized by the reduced structural and functional capability of the ventricles to fill with and pump blood. This condition presents with various symptoms such as difficulty breathing, fatigue, and increased jugular venous pressure (JVP) on physical examination. HF can be classified based on left ventricular function, using ejection fraction (EF) as a parameter. EF indicates the proportion of blood ejected from the heart with each heartbeat, with a normal value of 50% or greater.[20]

HF with a normal EF is known as HFpEF, also called diastolic heart failure. If the EF is less than 40%, the condition is termed heart failure with reduced ejection fraction (HFrEF), or systolic heart failure. Others with an EF between 40-49% may be classified as having heart failure with mid-range ejection fraction (HFmrEF).[20]

For patients with HF who are not in an emergency setting, a natriuretic peptide test can help determine the need for echocardiography. In acute cases, an immediate diagnosis of HF is necessary to identify any cause of symptoms. Patient's previous medical records, potential triggers, clinical evaluation, and additional tests such as electrocardiograms, chest X-rays, laboratory tests, and echocardiography should be noted to diagnose.[20]

The diagnosis of HFpEF can be confirmed by elevated natriuretic peptides (B-type natriuretic peptide [BNP] >35 pg/ml and/or NT-proBNP >125 pg/ml), and cardiac structural or functional abnormalities indicating HF. If the diagnosis remains uncertain, a stress test or invasive approach of left ventricular filling pressures can be performed.[20]

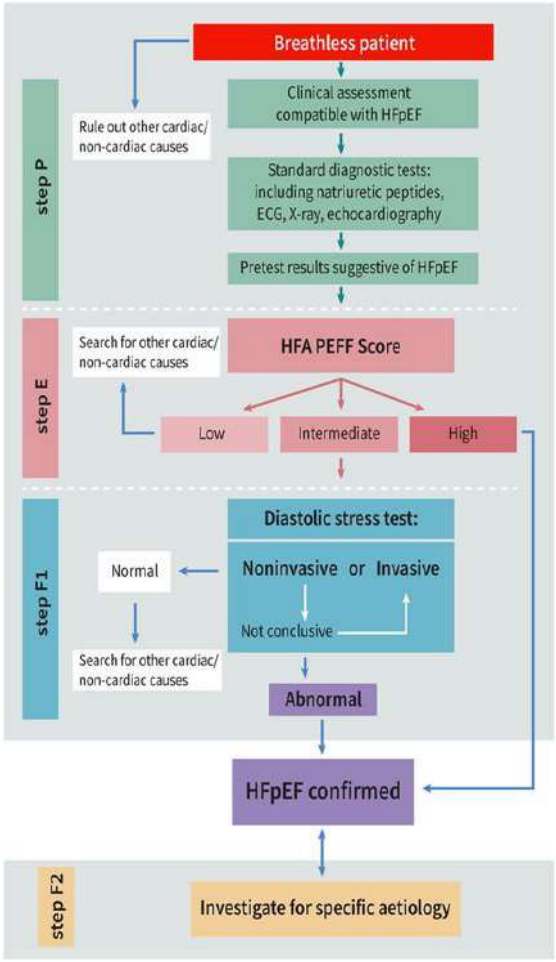

Figure 4. Flowchart of the HFA-PEFF diagnostic algorithm[21]

In 2021, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) developed a scoring system to diagnose HFpEF. This score includes functional, morphological, and biomarker domains, with each domain containing major and minor criteria. A major criterion scores 2 points, while a minor criterion scores 1 point. Each domain can contribute a maximum of 2 points if major criteria are met, or 1 point if only minor criteria are met.[21]

OHS in HFpEF

OHS is a condition that can cause shortness of breath, right HF, and severe PH, yet it remains underdiagnosed. Warricker, et al reported a case of a young woman experiencing severe PH and right HF who recovered after being diagnosed with OHS and receiving appropriate treatment.[22]

Similarly, another case reported by Terla et al was about a 53-year-old male experiencing right ventricular dysfunction, PH, and BNP levels of 160 pg/ml, without a history of smoking, and his lung function tests did not indicate any obstructive or restrictive lung disease. A pulmonary CT angiography was conducted, but no abnormalities were found. Therefore, chronic obstructive pulmonary disease, pulmonary embolism, or interstitial lung disease were ruled out. However, transthoracic echocardiography revealed moderate pulmonary hypertension, suggesting OHS as the underlying cause.[22]

OHS is associated with Grade 3 PH.[24] Recent studies reported about 52-68.8%[25,26] of OHS cases with PH. Right heart catheterization is considered the gold standard for diagnosing PH. However, transthoracic echocardiography is frequently used for assessment and observation because it is non-invasive,

affordable, accessible, and reliable to diagnose.[27]

The underlying causes of PH and right HF (with normal EF) in OHS patients are believed to be long-term daytime and nighttime hypoxia, hypercapnia, and acidosis. Additional conditions contributing to PH in these patients include restrictive pulmonary disease resulting from severe obesity and significant fluctuations in pressure within the thoracic cavity during the respiratory cycle owing to increased resistance in the upper airway. Obstruction in the upper airway leads to intense negative pressure within the thoracic cavity during inspiration, which boosts venous return and right ventricular filling, causing the intraventricular septum to shift leftward. As a result, left ventricular (LV) filling is reduced, leading to a lower stroke volume.[25]

MANAGEMENT

Positive Airway Pressure Ventilation

Positive airway pressure (PAP) works to keep the airway from collapsing, acting as a pneumatic splint, and has been the primary treatment for OHS. PAP can be delivered consistently throughout the breathing cycle, known as continuous PAP (CPAP), or varying pressures during inspiration and expiration referred to as bilevel PAP (BiPAP) or non-invasive ventilation (NIV).[16]

BiPAP aids in reducing the effort required for breathing, relieving the pulmonary muscles, and improving gas exchange, which results in higher O_2 levels and lower CO_2 levels.[16] Held et al reported patients with severe PH due to alveolar hypoventilation, who showed significant improvement after 3 months of NIV.[28]

CPAP provides a steady pressure throughout the breathing cycle to prevent obstructive apneas and hypopneas, without extra ventilatory support like NIV does. However, CPAP can still help to clear CO_2 that has built up during prolonged complete or partial obstructive events during sleep.[1]

Recent research has shown a substantial improvement of PAP therapy in fewer lengths of stay in hospital, management of sleep disorder breathing, and in the measures of the quality of life. The pulmonary function metrics, performance on the 6-minute walk distance test, and echocardiographic outcomes also showed a significant improvement.[26,29,30]

There is no definitive evidence showing one mode of PAP therapy is superior to the other. The choice typically relies on various factors, including the type of obstructive events of hypoventilation during sleep, the complexity of adjustments, and the cost.[1]

According to American Thoracic Society guidelines, patients diagnosed with OHS who are in stable condition should receive PAP therapy during sleep. For patients diagnosed with both OHS and severe OSA (AHI >30), CPAP is preferred as the primary treatment over NIV.[31]

If CPAP is not tolerated due to air leakage or discomfort, or if hypoventilation and desaturation episodes do not improve, it can be replaced with BiPAP. The target

SaO_2 for patients is >90%. If this target is not reached despite eliminating obstruction and hypoventilation, oxygen supplementation can be added.[31]

For hospitalized OHS patients with respiratory failure, NIV should be initiated before discharge, with PAP therapy titrated slowly over the first three months after discharge.[31]

A multicenter randomized controlled trial (RCT) in Spain involving stable patients with OHS and severe OSA, found that NIV and CPAP have comparable long-term effectiveness. Since CPAP is less complex and more cost-effective, it may be the preferred first-line PAP treatment option until further research is conducted.[32]

In addition, a recent systematic review and meta-analysis comparing the effectiveness of PAP treatments on OHS revealed that BiPAP provided the greatest improvement in hypercapnia and objective sleep patterns, including an increase in the percentage of paradoxical and deep sleep.[33]

Weight Loss Strategies

American Thoracic Society guidelines advised to reduce body weight by 25-30% through lifestyle modifications or bariatric surgery to improve hypoventilation.[31] Weight loss improves sleep-disordered breathing, OHS, and cardiometabolic health. Bariatric surgery is more effective than lifestyle modifications for achieving significant weight loss.[34]

A recent systematic review of weight loss interventions for patients with OHS showed that a comprehensive weight loss program successfully lowers body weight but shows no marked benefits compared to standard care (such as diet and exercise advice provided during ambulatory visits). Contrary, the bariatric approach is linked to more efficient weight loss, subsidence of OHS, lower OSA severity, and improvements in pulmonary artery pressure, gas exchange, and daytime drowsiness.[34]

OHS with HF

The Pickwick project showed that PAP therapy improves PH and LV diastolic function. Both NIV and CPAP treatments significantly lowered systolic pulmonary artery pressure, though right ventricular function remained unchanged in either PAP group. No notable changes were observed in left ventricular hypertrophy or systolic function; however diastolic function showed substantial improvement with PAP therapy.[35]

The principles for treating patients with HF and OHS are similar to those for patients without OHS, focusing on reducing congestive symptoms with diuretics.[36] However, it is crucial to address acute HF episodes in OHS patients carefully.[36]

Loop diuretics can increase serum bicarbonate levels, reducing the respiratory response and worsening hypercapnia in OHS patients. Studies have shown that carbonic anhydrase inhibitors, such as acetazolamide, are safe for OHS patients because they can prevent alkalosis by lowering bicarbonate concentration and enhancing respiratory responses.[36]

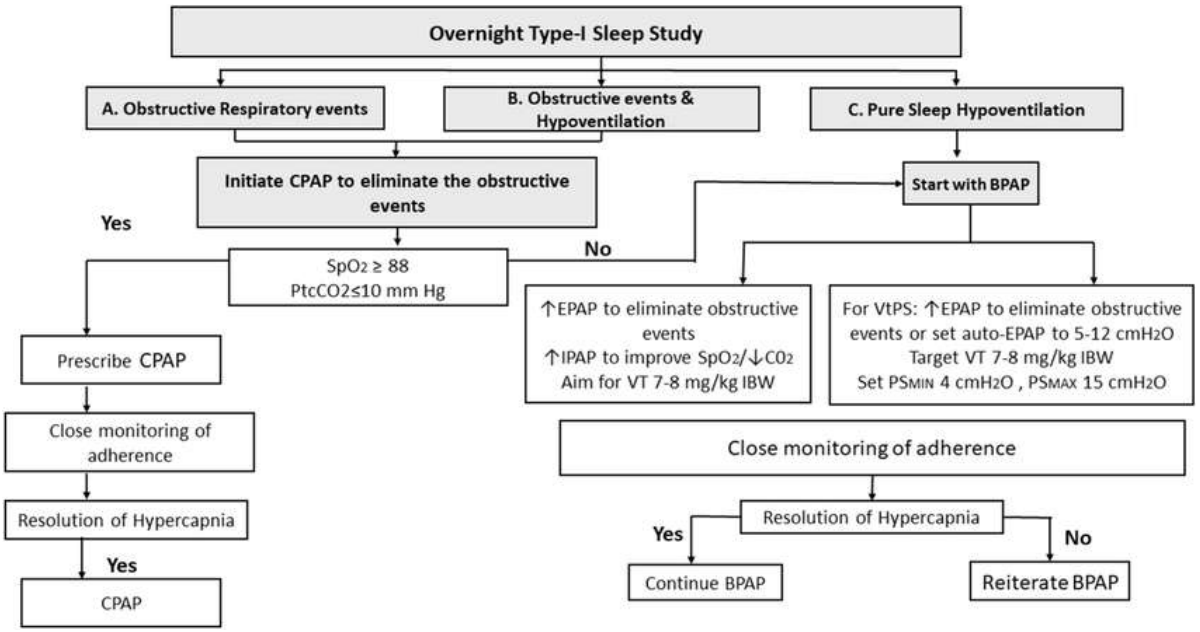

Figure 5. A Proposed Algorithm to Applying PAP in OHS Patients[37]

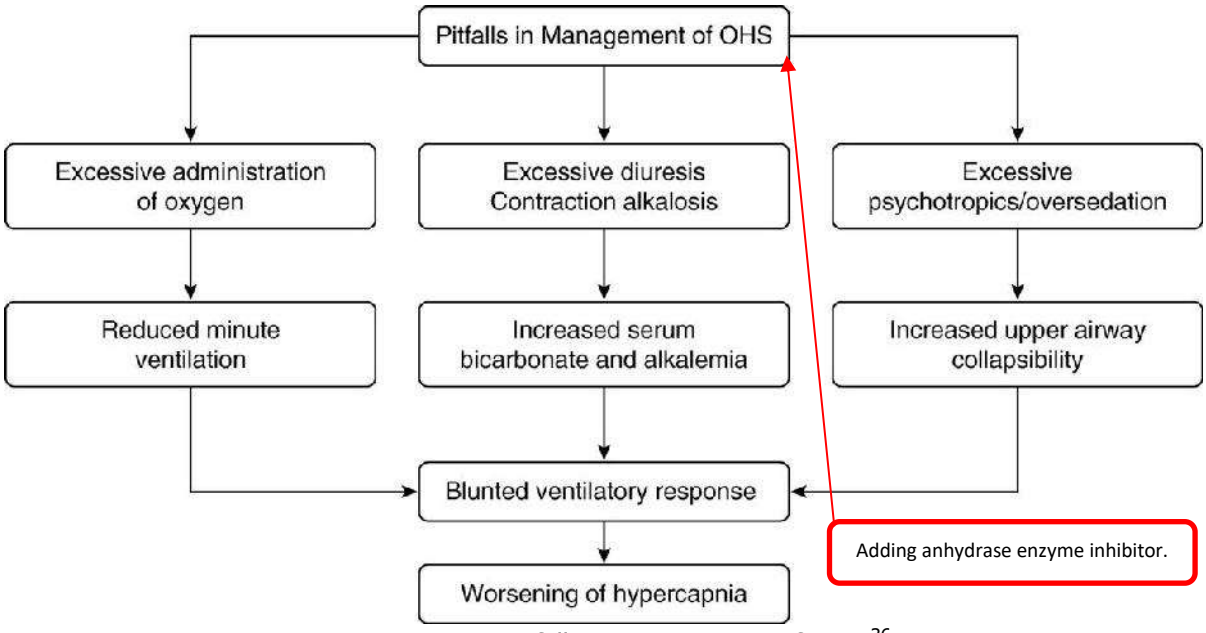

Figure 6. Pitfalls in Management of OHS.[36]

PROGNOSIS

Mortality rates in OHS were substantially higher than in OSA. The 5-year mortality rates were 15.5% in OHS and 4.5% in OSA. OHS patients had a twofold increase in mortality risk and a 1.86 times risk of having a cardiovascular event.[5]

Another study showed the 5- and 10-year survival rates were lower in the OHS patients compared to OSA patients, with rates of 83% versus 96% at 5 years and 74% versus 91% at 10 years. Moreover, ventilation therapy by CPAP and BiPAP has significantly lowered mortality in all patients.[38]

CONCLUSION

OHS is a frequently underrecognized cause of HFpEF. Its pathophysiology includes increased mechanical loads on the respiratory system, elevated airway resistance, and reduced pulmonary compliance, culminating in pulmonary artery remodeling, PH, and right heart failure.

Early diagnosis and timely intervention are crucial to preventing deaths from heart failure. Preliminary screening for OHS can be performed by utilizing basic tests like pulse oximetry and serum bicarbonate levels, followed by ABG analysis to rule out OSA.

PAP ventilation remains the cornerstone of treatment for OHS, particularly in HFpEF. Long-term management strategies, including significant weight loss, improve vital capacity and reduce chronic hypercapnia.

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