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Original Article

Correlation of Smoking Habit and Level of Nicotine Dependence in University Students

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Abstract

Background: Smoking habits are still a global problem. One of the harmful compounds in cigarettes is nicotine which gives a dependence effect on its users because long-term exposure can cause desensitisation of nicotinic acetyhlcoline receptor. This study aimed to determine the correlation between degree of smoking habit and level of nicotine dependence in actively smoking university students.

Method: A cross-sectional study was conducted using questionnaires, consisted of relating factors questionnaire (age, BMI, academic major, allowance, family smoking habits, and social environment), degree of smoking behavior questionnaire (Brinkman Index/IB), and Fagerstorm Test for Nicotine Dependence/FTND questionnaire.

Results: There were 124 active smoker university students included in this study. This study found that the higher the BI score, the higher the FTND score (P<0.001; r=0.420). In addition, this study also found that there were positive correlations between age (P=0.009; r=0.223), personal income (P=0.003; r=0.261), and academic major (P=0.042) with the levels of smoking habit. There was also correlation between allowance (P=0.005; r=0.249) with level of nicotine dependence.

Conclusion: These results indicate a significant moderate correlation between smoking habit with nicotine dependence among university students.

Keywords: Brinkman, Fagerstorm, nicotine, smoker, student.

INTRODUCTION

Smoking is still a major health problem in the world. Based on the World Health Organization (WHO) data, there were more than 1.1 billion tobacco smoker out of 7.38 billion population in 2015.[1,2] As many as 80% of the 1.1 billion smokers live in low to middle income countries.[3] Based on the 2018 Riset Kesehatan Dasar (Riskesdas) data, the prevalence of smoking in Indonesia is also high at 28.8%, although there is a decrease number

compared to the 2013 Riskesdas data (29.3%).[4]

While looking at the age group, many Indonesian smokers are also in their teens or young adults. Proportion of smoker above 10 years old are 12.7% in daily smoker and 6.9% in occasionally smoker among ages 15-19 years. Another group of ages 20-24 years have proportion of smoker are 27.3% (daily smoker) and 5.9% (occasionally smoker) based on Riskesdas 2018.[5]

Data from Global Adult Tobacco Survey (Indonesia report 2011) proportion of male smokers are still greater women, with the number of active male smokers aged over 15 years of 76.1%. This data shows the high number of active male smokers in young age groups in Indonesia.[6]

Cigarettes contain many harmful substances, including nicotine, which gives an addictive effect on smokers.[7] The WHO declares that more than 6 million people died from active smoking.[3] Data from Indonesia also shows a high prevalence of smokers among adolescents and young adults, where students included in those group.

However, there is no data regarding the degree of smoking habits and the level of nicotine dependence on active smoker among university students. Therefore, this study aimed to look for the correlation between smoking habits and the level of nicotine dependence on active smoker students at university in Depok

METHOD

This is a cohort prospective study, conducted in March-July 2020. This study was conducted on pulmonary TB patients who were treated at MDR-TB Polyclinic at dr. Saiful Anwar Malang. The inclusion criteria in this study were patients diagnosed with rifampicin-resistant pulmonaryTB, aged 18-65 years, who were willing to participate in the study and signed an informed consent. Patients who had received anti-MDR-TB drugs for ≥1 month, patients with Human Immunodeficiency Virus (HIV) and pregnant women were not included in this study.

The minimum sample size was 38. Samples were obtained by means of consecutive sampling that fulfilled the criterias. In this study, 39 subjects who met the inclusion and exclusion criteria were subjected to Acid Fast Bacillus (AFB) sputum smear and IL-2 levels measurement on day 0 and day 30 after receiving MDR-TB treatment (Shorter Regimen/Longer Regimen).

This was a cross-sectional study conducted in the university in Depok from July to August 2019. The research instrument used in this study consisted of three types of questionnaires. The first one is a questionnaire to obtain demographic data, including age, height, weight, allowance, academic major, smoking habits of the nuclear family, and smoking habits in the social environment.

The second questionnaire is a questionnaire to assess the degree of smoking habit (the Brinkman Index/BI). The last one is Fagerstorm Test for Nicotine Dependence (FTND), a questionnaire that is used to assess an individual's level of dependence on nicotine. This test is designed to calculate the level of dependency on nicotine and its relationship with smoking activity.

The smoking activity in this questionnaire includes quantity, motivation, and also symptoms of dependence on nicotine consumption in cigarettes or other nicotine-containing products.[17] This test has a score range of 0-10. The higher the score obtained, the higher the level of the person's dependence on nicotine. The independent variable in this study was the degree of smoking habit, which is calculated using the Brinkman Index. The dependent variable was the level of nicotine dependence.

The subjects included in this study were undergraduate students at the university in Depok, male, and active smoker. Subjects who were willing to participate in the study must sign an informed consent form. The total sample was 124 subjects obtained from students of the natural sciences and social sciences. The sample size was calculated using a single data proportion formula, with the prevalence of smokers was 67% as it was the prevalence of male smokers in Indonesia according to the 2011 GATS. The subjects who met the research criteria were consecutively recruited in the study until reached the minimum sample size.

The data is then processed and analyzed. Numerical data will be analyzed with Pearson Correlation, if the data is normally distributed or Spearman Correlation, if the data is not normally distributed. Meanwhile, categorical-numeric data will be analyzed by t test, if the data is normally distributed or by Mann-Whitney test, if the data is not normally distributed.

RESULTS

The characteristics of the subjects are shown in Table 1, including data on age, body mass Index (BMI), academic major, allowance, family smoking habits, and social environment.

Table 1. Characteristic of the Study Subjects

Characteristics	N (%)
Age (years); median (range)	20 (17–27)
Body mass Index (BMI); mean±SD	24.28±4.58
Underweight (<18 kg/m^2)	6 (4.8%)
Normal (18-25 kg/m^2)	69 (55.6%)
Overweight (25-27 kg/m^2)	13 (10.5%)
Obese (>27 kg/m^2)	36 (29.1%)
Academic major	
Natural science	48 (38.7%)
Social science	76 (61.3%)
Allowance (per week)	
Rp0 – Rp500.000	28 (22.6%)
Rp500.000 – Rp1.000.000	46 (37.1%)
Rp1.000.000 – 1.500.000	16 (12.9%)
>Rp1.500.000	34 (27.4%)
Having an active smoker in nuclear family	
Yes	81 (65.3%)
No	33 (34.7%)
Having an active smoker in social environment	
Yes	124 (100%)
No	0 (0%)

The data were taken within 3 weeks and obtained 124 subjects which come from students of the natural sciences and social sciences. In addition to BMI, this study also obtained data of the mean of height (172.31±6.08 cm) and weight (72.22±14.93 kg). Distribution of smoking habits based on the Brinkman Index (BI) has three categories: mild (BI: 0 – 200), moderate (BI: 201 – 600), and heavy smoker (BI >600).

This study showed the median of BI was 46.5 and the minimum – maximum range was 1-280. We found total of 118 students (95.2%) were mild smoker and only 6 students (4.8%) were moderate smoker. There were no heavy smoker founded among smoker students. Mild smoker were mostly found from social science students (56.5%) compare from natural science students (38.7%). In other hand, moderate smoker students only found from social science students.

The level of nicotine dependence was measured by the Fagerstrom questionnaire, which contains 7 questions and then converted into a score that has a minimum and maximum range of 0-10. In addition, this score is categorized into 4 groups: low dependence (0-2), low to moderate dependence (3-4), moderate dependence (5-7), and high dependence (8-10). The normality test was carried out using the Kolmogorov-Smirnov test, and the data was not normally distributed (P<0.001). The median Fagerstrom score was 3 with a range of 0-9. Figure 1 showed the proportions of nicotine dependence level in two academic major (natural and social sciences).

This study also looked for the correlation between age, BMI, allowance with the levels of smoking habits (as Brinkman Index). A significant weak positive correlation was seen between age and allowance with Brinkman Index (P=0.009 and P=0.003 respectively) (Table 2).

Table 2. Correlation between Age, BMI, and Allowance with Brinkman Index

	Age	BMI	Allowance
Brinkman Index	r=0.223* P=0.009* n=124	r=0.099** P=0.276** n=124	r=0.261* P=0.003* n=124

Note: *Spearman correlation **Pearson correlation

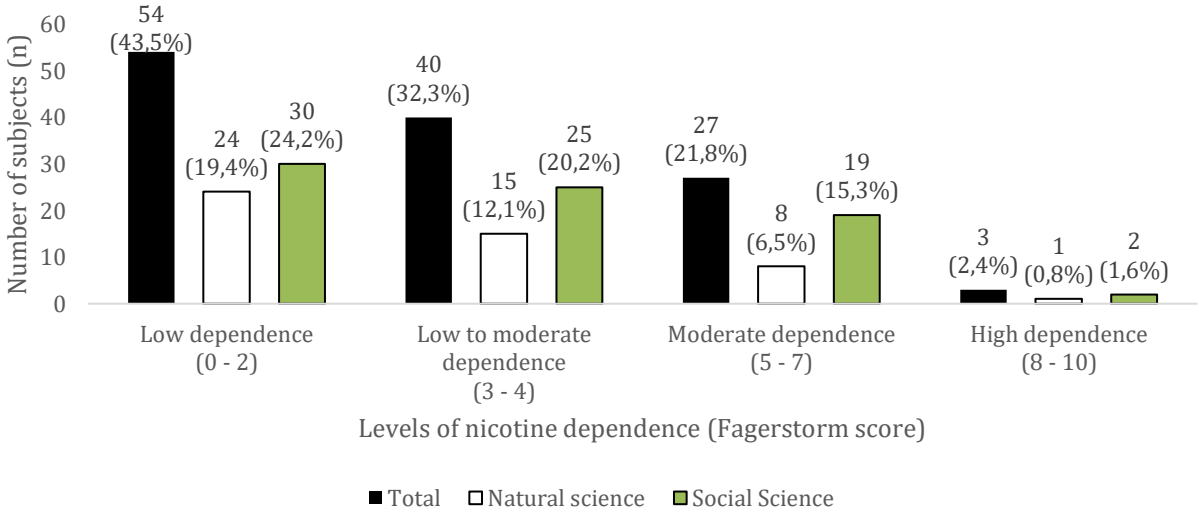

Figure 1. Proportion of nicotine dependence level (Fagerstrom score)

Table 3. Correlation of Academic Major and Smoking Habits in Nuclear Family with the Levels of Smoking Habit

Brinkman Index	Median (Range)	P
Natural science (n=48)	36 (2–200)	0.042
Social science (n=76)	60 (1–280)	
Having an active smoker in nuclear family (n=81)	50 (2–280)	0.212
No active smoker in nuclear family (n=43)	40 (1–204)	

Note: Mann-Whitney test.

Table 5. Relationship between academic major and smoking habits in nuclear family with Fagerstrom score

Fagerstrom score	Median (Range)	P
Natural science (n=48)	2.5 (0 – 8)	0.196
Social science (n=76)	3 (0 – 9)	
Having an active smoker in nuclear family (n=81)	3 (0 – 8)	0.370
No active smoker in nuclear family (n=43)	3 (0 – 9)	

Note: Mann-Whitney test.

In this present study, there was a statistically significant difference between academic major and Brinkman Index (P=0.042), yet no statistically significant difference was seen between the family smoking habit and Brinkman Index (Table 3).

No statistically significant correlation was found between age (P=0.458) and BMI (P=0.149) with Fagerstrom score. However, there was a significant weak correlation between allowance with Fagerstrom score (r=0.249; P=0.005) (Table 4).

Table 4. Correlation between Age, BMI, and Allowance with Nicotine Dependence Level

	Age	BMI	Allowance
Fagerstrom score	r=0.067 P=0.458 n=124	r=0.130 P=0.149 n=124	r=0.249 P=0.005 n=124

Note: Spearman correlation

We also did not found significant difference between the academic major and the smoking habits in nuclear family with the Fagerstrom score as in Table 5. This study found that levels of smoking habit (Brinkman Index) was significantly correlated with the levels of nicotine dependence (Fagerstrom score) (r=0.420; P<0.001) using Spearman correlation.

DISCUSSION

This present study showed median age of active smokers were 20 years old with a range of 17-27 years. This in in accordance with a study by Sutfin et al[8] which reveals that the mean age of smoking college students in United States was 20.5±2.9 years. Mean BMI of our subjects was 24.28±4.58 kg/m^2. This result is higher than the result from Hastuti et al who found that the mean BMI of smoking students was 22.30±4.39 kg/m^2.[9] Number of obese subjects in this study was also higher than Hastuti et al (29.1% vs 14.0%).

All subjects in this study have friends who are also active smokers. Meanwhile, 65.3% have active smokers in the nuclear family. A study by Resen also found similar results that the proportion of smoking students who have smoking parents are greater than those who have non-smoking parents.[10]

The Brinkman index in this study was relatively milder than other study because of the subjects were young population (teenager and young adults). These results are in line with the study by Amelia et al which found similar differences in the Brinkman index according to the subject's age group.[11]

This study revealed that the level of nicotine dependence on active smoker students was relatively low. This can be seen from the decreasing number of subjects from low to high nicotine dependence groups. Salameh et al also found similar results from 603 Lebanese students who filled out the Fagerstorm questionnaire.[12] The mean Fagerstrom score was 3.46±2.42 and there was a downward trend from light to heavy smokers. Lamin et al also reported similar results from student in Penang.[13]

We found a significant positive correlation between age and allowance with levels of smoking habit (Brinkman index). A similar result was seen in a study by Amelia et al.[11] The older a person is, the longer the duration of smoking. However, the correlation in our study was weak due to the younger age of our subjects (17-27 years). Perelman et al investigate the relationship between personal income of adolescents aged 14-17 years and smoking habit.[14] Adolescents who have the highest income had a tendency to become a daily smoker (OR=3.51), weekly smokers (OR=4.55), and had a higher smoking intensity (cigarette consumption) compared to the ones who have the lowest income.

Allowance was positively correlated to the levels of smoking habit (Brinkman index). Low-income adults are prone to have stress and psychological burden. Meanwhile, it is suspected that allowance has no effect on stress and psychological burden on students. As a result, students tend to have higher nicotine dependence as their allowance increases.

Smoking habit in social science students in this present study was significantly higher than the natural science students. Our study also found that there was no significant difference between family smoking habit and a person's smoking habit. Binita et al showed that there was no relationship between the number of smokers in the family and smoking behavior in vocational students in Semarang.[15]

Despite of that, Mays et al revealed that exposure of active parental smoking was related to offspring smoking habit, and the effect increases with longer exposure.[16] However, Resen elucidated that social environment had a higher impact than parental smoking.[10]

This study found no correlation between age and BMI with the level of nicotine dependence. However, several studies stated that there is a relationship between age and the level of nicotine dependence (Fagerstorm questionnaire).[17,18] Study by Li et al there was an inverse U-shaped relationship where middle-aged smokers (45-64 years) had higher level of nicotine dependence than those of young age (<45 years) and old age (≥65 years).[17] In addition, Park et

al found that the peak age to have a significant highest level of nicotine dependence was 50 years.[18]

Our study did not find a significant correlation between academic major and family smoking habits with the level of nicotine dependence. Binita et al stated that the number of smokers in family was no related to one's smoking habits.[15] In contrast with this author, Mays et al showed that longer duration of exposure to smoking parents will increase likelihood the adolescents become regular smoking.[16] Gilman et al clarified that parental smoking is associated with risk of adolescents' smoking initiation.[19]

This study found that the level of smoking habit was correlated with the level of nicotine dependence. This is in accordance with the theory that nicotine causes dependence to smokers. Nicotine induces dopamine release from dopaminergic neuron in the ventral tegmental area and nucleus accumbens. Dopamine provides a reward sensation as calming and happy feeling.[20]

Nicotine augments glutamate release that induces dopamine release, and gamma-aminobutyric acid (GABA), which inhibit dopamine release. Prolonged exposure to nicotine will desensitize nicotinic acetylcholine receptors. As a result, the release of glutamate remains high, whereas the release of GABA decreases. Therefore, smokers who develop this effect will experience withdrawal symptoms when they give up smoking because of low nicotine level.[20]

This phenomena proves that the greater levels of smoking habit, the higher levels of nicotine dependence. This is consistent with previous study by Lamin et al that found significant correlation between the levels of smoking habit and the levels of nicotine dependence.[13]

However, some limitations need to be acknowledged from this study. First that, this study only examine the effect of smoking habit to nicotine dependence without considering other confounding factors. Another, that recall bias might happen when the subjets fill out the questionnaire.

CONCLUSION

This study found that students' smoking habits were in mild level, whereas nicotine dependence was in low-moderate levels. There was a moderate correlation between smoking habit and nicotine dependence. Our subjects tend to have low levels of smoking habit and nicotine dependence. Therefore, it would be easier to educate them as early as possible to stop smoking. Educational and enganging smoking cessation campaign should be carried out earlier in students as it would be difficult to stop smoking when someone has smoked for a long time and develop nicotine dependence.

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Original Article

Relationship Between Nutritional Status, Physical Activity, Type of Work and Smoking Activity with Fitness Level Measured by 6-Minute Walking Test on Non-staff Employees of Universitas Indonesia, Depok

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Abstract

Background: Fitness is inextricable to health and has a significant correlation with the habits and behaviour of individuals such as dietary practice, sedentary behaviour, physical activities, and smoking habits. Many ways can be used to assess an individual fitness level, one of them is using the 6-minute walking test. This study aims to find the correlation between smoking intensity, nutritional status, occupation, and physical activity with the fitness level of outdoor janitors in Universitas Indonesia, Depok.

Method: The research method was the cross-sectional design. The determination of the subjects was carried out by a consecutive sampling method. The data obtained results from the assessment of nutritional status, occupation, physical activity, and smoking intensity, as well as result from the 6-minute walking test. Univariate data analysis was used to assess the distribution of subjects based on sociodemographics, nutritional status, physical activity, occupation, and smoking activity. Furthermore, categorical correlative tests used were Man-Whitney, Kruskal-Wallis, and Fisher's Exact test.

Results: The subjects obtained are 109 outdoor janitors from UI, Depok in which 59.6% age 18-44 years old, and 56% are male. Based on the correlative test between the fitness level and the nutritional status, value of P=0.086, as value of P between the physical activity and the fitness level is 0.0523. No significant correlation between fitness level and occupation based on location of the job, duration of work and based on the work time (P=1.00; P=1.00; P=0.108). The correlation between smoking intensity with the fitness level has value of P=0.681.

Conclusion: There is no significant correlation between nutritional status, physical activity, type of work, and smoking intensity with the fitness level as measured by the 6-minute walking test method for outdoor janitors of UI, Depok.

Keywords: 6-minute walking test, smoking, nutritional status, occupational medicine, physical exercise

INTRODUCTION

Sedentary behavior can cause various chronic diseases such as heart disease, ischemic stroke, metabolic syndrome, cancer, non-insulin-dependent diabetes mellitus, osteoporosis, respiratory disease, and mental health disorders. According to World Health Organization (WHO), in 2016, 27.5% of adults worldwide did not do enough physical activity.[1] The most recent Baseline Health Research 2018 in Indonesia found that 33.5% of the Indonesian people have a low level of physical activity.[2]

The type of work also influences this sedentary behavior. Currently, workers spend 76% of their working time or 6 hours per day sitting. In one study, workers who sat for more than 11 hours per day had a 40% higher risk of dying within three years and a 50% higher risk of developing heart disease, compared to workers who sat for less than 4 hours.[3,4] Sedentary activity and smoking can also trigger cardiovascular disorders, cancer, and lung disease.[5,6] There are around 1.1 billion smokers worldwide, with the majority being male.[5] In ASEAN, Indonesia has the highest percentage of smokers amounting to 46.46% which continues to increase from year to year.[7]

A person's health status is also greatly influenced by nutritional status. Indonesia is currently experiencing multiple nutritional problems, namely malnutrition and overnutrition.[8] Lack of physical activity, types of work related to sedentary behavior, smoking activity, and a person's nutritional status are thought to affect a person's level of fitness. One of the simple, easy, inexpensive, and safe methods that can be used to test a subject's cardiorespiratory capacity and the effect of submaximal exercise on a person is the 6-minute walk test.[9–14]

There is no statistical data regarding the level of fitness in non-staff employees of the University of Indonesia Depok, thus encouraging researchers to find out the relationship between nutritional status, type of work, smoking activity, as well as routine, and level of physical activity to fitness level as measured by the 6-minute walk test method. This study aims to scrutinize the characteristic data of these variables and the level of fitness as measured by the 6-minute walk test of Non-staff Employee of Universitas Indonesia, Depok.

METHOD

This study was a cross-sectional survey conducted in July 2019 in Balairung, Universitas Indonesia. This survey was conducted in four steps: 1) self-filled questionnaire about smoking activity, 2) cardiopulmonary examination before walking test, 3) 6-minute walking test, 4) cardiorespiratory examination after the test. A total of 104 participants joined this survey based on inclusion criteria with a consecutive sampling method with the inclusion criteria were; 1) janitor employees in Universitas Indonesia, Depok, 2) consent to take part in the study. The exclusion criteria were; 1) physical

limitation to conduct 6-minute walking test, 2) pregnant women, 3) incomplete data. We finally included 109 subjects that eligible to participate in this study.

The independent variables in this study were gender, age, educational status, physical activity level, type of work, nutritional status, and smoking activity of subjects. The other data collected in this study were body height, body weight, Peak Expiratory Flow Rate (PEFR), oxygen saturation, blood pressure, and heart rate. Those data were obtained using self-filled questionnaire and physical examination. The questionnaire consisted of demographic data, type of cigarette, duration of smoking, and amount of cigarettes per day. Smoking activity classified into some categories (Table 1).

The dependent variable was physical fitness measured based on 6-minute walking distance. Physical fitness classified as normal, poor, and very poor. Normal defined as 85%, poor fitness 77%-85%, and very poor <77% based on ratio percentage actual subject's distance per predicted distance using Nury's formula as follow: 586,254 + 0,622 BW (kg) – 0,265 BH (cm) – 63,343 gender* + 0,117 age. (*0 for male, 1 for female).[3] The study by Nury et al assessed the distance in healthy subjects. Walking distance is an output from 6-minute walk test (6MWT) that conducted using American Thoracic Society (ATS) guideline. The 6MWT is a simple, safe, valid, and reliable test to measure respiratory function.

In the correlation test, the researchers connected each type of work, namely duration, location, shift time, and how to work with fitness levels. Researchers prefer to use the Pearson test because the number of crosses between variables is more than 2x2. Then the next test cannot be used after getting the output from SPSS that there are more than 20% of cells whose value is less than 5 so they cannot use the test.

Furthermore, the most appropriate test to relate variables based on conditions of more than 20% of the number of cells less than 5 is Fisher's exact test. The researchers recategorized the two variables whose number of crosses was more than 2x2 because in Fisher's test to calculate the relationship between variables, 2x2 crosses between variables were required. The recategorization carried out on the level of fitness is to unite the unfit and very unfit groups.

RESULTS

The sociodemographic background of all subjects is outsourcing staff at UI Depok. Out of 109 subjects, 65 subjects (59.6%) of them are aged 18-44 years old and the rest are aged between 45-64 years. Based on gender, 61 subjects or 56% were male and 48 subjects or 44% were female. Their work units were divided into four, 1 subject (0.9%) worked as parking attendants, 11 subjects (10.1%) as gardeners, 93 subjects (85.2%) as janitors, and 4 subjects (3.7%) as garbage truck drivers.

The distribution of subjects based on fitness levels can be seen in Figure 1. The

109 subjects were divided into 3 different fitness levels, the results were 2 subjects or 1.83% are fit, 3 subjects or 2.75% have poor fitness level, and 104 subjects or 95.4% have very poor fitness level.

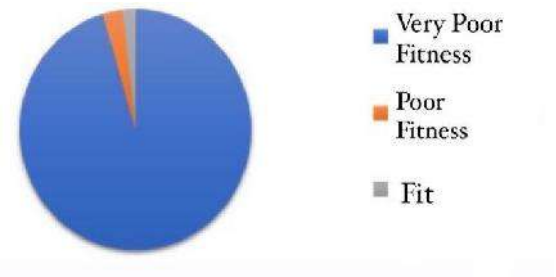

Figure 1. Distribution of Fitness Levels Measured with The 6-Minute Walk Test

Table 1. Relationship of Nutritional Status, Physical Activity, Type of Work, and Smoking Activity with Fitness Level

Variabel	Fitness Level			P
	Normal	Poor	Very Poor	
Gender				
Female	1	3	51	0,058*
Male	0	0	48	
Age (years old)				
≤25	1	2	14	0,05**
26-40	0	0	31	
>40	0	1	54	
Nutritional Status				
Underweight	1	1	9	
Normal Weight	1	2	55	0,086**
Overweight	0	0	15	
Obese	0	0	25	
Physical Activity Level				
Mild	0	0	9	0,523**
Moderate	2	1	65	
High	0	1	24	
Work Location				
Indoor	0	0	0	
Outdoor	2	3	99	1,00***
Both	0	0	2	
Vary	0	0	3	
Work duration				
≥8 hours	2	3	97	1,00***
<8 hours	0	0	7	
Shift				
Day	1	2	100	0,108***
Night	0	1	1	
Vary	1	0	3	
Work Type				
Physical	2	3	104	---
Non-physical	0	0	0	
Smoking duration (years)				
Non smoker	0	3	54	0,586**
≤10	1	0	25	
>10	0	0	20	
Number of cigarette per day				
Non smoker	0	3	54	
<10	1	0	19	0,708**
10-15	0	0	21	
>15	0	0	5	
Brinkman Index				
Non-smoker	13	16	28	0,681**
Smoker with mild IB	10	17	9	
Smoker with moderate IB	2	4	4	

Note: *Mann-Whitney test; **Kruskall Wallis test; ***Fisher's Exact Test

In Table 1, we can see the relationship between gender, age, nutritional status, level of physical activity, work activity, and smoking activity with fitness levels which are classified into: fit, not fit, and very unfit. Nutritional status was grouped into undernutrition, normal nutrition, overweight, and obesity based on the BMI of the subject. Work activities are divided into several subtypes, namely the location, duration, shift, and work type.

Smoking is divided into several parts, namely smoking duration (years), number of cigarettes consumed per day, and the Brinkman index. The smoking intensity is measured using Brinkman Index (BI) categorized into; non-smoker, smoker with mild BI (1-199), smoker with moderate BI (200-599), and smoker with severe BI (>600). But none of our subjects was categorized as smoker with severe BI.

Based on these data, only the age variable showed P<0.05 which indicates a statistically significant relationship between age and fitness level. Meanwhile, the other variables, which were tested using Man-Whitney, Kruskal-Wallis, and Fischer's test, showed no statistically significant correlation.

DISCUSSION

The results of this study indicate that if nutritional status is not correlated with fitness level (P>0.05), it means that nutritional status does not directly have a relationship with a person's fitness status. In this study, a person's status was measured by BMI. A study conducted in Brazil by RS Ferreira et al also showed that BMI was not associated with performance in walking and on tests and flexibility.[15]

Underweight individuals performed worse on tests of strength and endurance for sex, age, education level, and occupation compared to those who were underweight. While in a study conducted by Goins et al with research subjects American Indians showed that someone with a BMI value more than normal or has more nutritional status than obesity has the worst results in fitness and endurance tests using the standing method on the chair.[16] While the data obtained from SABE conducted on 2143 adults in the older age group did not find any relationship between fitness and nutritional status.[17]

The cut-off BMI that is set or used by each country is different in classifying nutritional status based on BMI. This shows that the relationship between BMI with fitness and physical performance can give different results based on the characteristics possessed by the subject group, both sociodemographic characteristics and characteristics from within the subject.[17]

In this study, the cut-off BMI used was adapted to the conditions of the Indonesian people, namely using the BMI standard from the Ministry of Health. Various sources mention the fact that nutritional needs are quite important to maintain health and endurance, including fitness. The decrease in endurance or strength can be described by the volume of muscle mass. BMI is highly correlated with fat-free body mass in adults. Lower BMI

values can result in decreased of muscle mass resulting in reduced strength and endurance. Therefore, maintaining a good nutritional status is very important to maintain strength and functional capacity.[17,18]

Various physical activity guidelines, for instance, the AHA (American Heart Association) Recommendations for Physical Activity, state that to achieve physical fitness or to maintain health, the recommended physical activity is (1) moderate-intensity physical activity of at least 150 minutes per week, or (2) high-intensity physical activity with a minimum duration of 75 minutes per week.[19]

The fitness level of the subjects was measured with the 6-minute walk test. The 6-minute walking test is used extensively to evaluate the advantage of physical activity on physical endurance in carrying out daily activities. The 6-minute walk test can measure functional capacity that reflects daily physical activity level.[20]

In this study, to know the level of physical activity of the subjects, the researchers used the International Physical Activity Questionnaire (IPAQ) – Short Form to assess the physical activity routine performed by the subject. The IPAQ Form was modified by translating it into Indonesian, adding a few keywords to help the subjects understand the question, as well as adding questions about what physical activity the subject often does.

In interpreting the answers of the subjects, IPAQ Scoring used protocol with a few modifications, of which answers regarding walking and sitting were not scored because they were not physical activity. The result is that most of the subjects have a moderate level of physical activity. This means the majority of them do vigorous-intensity physical activity for 3 or more days a week, moderate physical activity for 5 or more days a week, or a combination of moderate and vigorous physical activity for 5 or more days in a week, all for at least 30 minutes per day and thus reach a minimum of 600 MET a week. A correlation test between the physical activity level and physical fitness of the subjects was performed, and it was known that there was no significant relationship between the subject's level of physical activity and the fitness level of the cleaning staff outside the UI Depok building.

In addition, the subjects' physical activity routine analysis showed that 90.2% of the subjects did physical activity according to the AHA recommendations, while the rest did not. Most of the physical activity performed by the subject is the activities they do while working. Although most of their physical activity routine satisfies the AHA recommendations, the majority of the subjects are very unfit. Analysis of fitness level used the formulation of the 6-minute walking test that applies to Indonesian anthropology. Based on the statistical tests, there is neither significant nor positive correlation between the suitability of physical activity routine with AHA recommendations and the level of fitness of the subjects.

This can be explained by the fact that the activities the subjects do are carried out

at work so it is not sufficient in intensity, volume, and duration to deliver improvement in fitness levels. Because their job demands them to be physically active, only a small proportion did more physical activity outside of work. Therefore, a high level of physical activity at work does not lead to a high level of fitness. A heavier load of physical activity at work is thought to result in lower fitness level due to persistent fatigue and chronic changes due to repetitive overwork. It takes physical activity outside of work to be able to provide a high level of fitness.[21] It can be concluded that the hypothesis is rejected.

After getting the distribution of the type of work and fitness level the researcher analysed for correlation between these two variables. It's better to put this information in the methods section instead of in the results section. This study uses the chi-square test to determine the value of P of the relationship between the two variables. The use of the kai square test is also because the two variables, both type of work and fitness level, are categorical data.

The recategorization carried out on the type of work is only carried out on the location and shift of work time because the total duration of work and the way of working have met the 2x2 crossing criteria. At the work location, because there are no workers who work only indoors, the recategorization that is put together is uncertain and can be both. Meanwhile, in the shift time, the recategorization was carried out in the afternoon shift and was erratic.

Based on this fisher test, it was found that the relationship between fitness level and work location, and duration of work had the same value of P. This value shows that there is no relationship between fitness level and work location and fitness level with a duration of work ($P>0.05$). Furthermore, the relationship between fitness level and shift work time also does not have a relationship with $P=0.108$ which also states that there is no relationship between the two variables. The relationship between the level of fitness and the way of working cannot be determined because the way of working on the subject is constant, namely physical work. This relationship becomes information that needs to be known because there is still a lack of studies that discuss the level of fitness and this type of work.

In the comparison between workers with different locations, it can be seen that more subjects are classified as fit who work outdoors compared to workers located outside and indoors. Previously, the researchers discussed in the literature review that outdoor or outdoor workers have a higher risk of disease compared to indoor workers, so it is evident that in the results of the study most of the workers who work outdoors show a very unfit fitness level.[22–24]

However, the results of subjects classified as fit are also in outdoor workers, this is because workers with outdoor locations have a higher tendency to avoid sedentary or sedentary behavior. This behavior will improve fitness through

increased physical activity so that the volume of oxygen that is able to be processed by the body in carrying out the respiration process is trained so that the distance traveled by the subject during the 6-minute walk test has results that are classified as fit.[22–24]

Likewise, subjects classified as fit who work more than equal to eight hours at the same time are located outdoors and have a tendency to have higher physical activity than subjects who work less than eight hours. However, along with the increasing number of hours of work, a person has the potential to feel unwell that cause fatigue to work. So that most of the subjects who worked more than eight hours in this study were classified as very unfit. Different results from the literature can be found in the comparison between fitness and shift work time. The results of this study indicate that the number of fit subjects that work in the morning is the same as those who has erratic shifts.[22–24]

After being observed specifically on subjects who work in erratic shifts and have the results of a 6-minute walk test classified as fit, it is recorded that the subject has normal cardiorespiratory characteristics, including blood pressure, oxygen saturation, and pulse rate before and after the 6-minute walk test. The argument that supports the susceptibility of workers at uncertain times to contract diseases is that the immune system is affected by suboptimal work of white blood cells. However, each individual's immune system will respond differently and the subject proved that with completely normal cardiovascular characteristics, the subject still has a fit 6-minute walk test result.[22–24]

How to do work in which the research subject has 100% physical work results also turns out to be only 2% of all subjects who work physically with a fit fitness level group, while the rest are classified as unfit and very unfit. It can be seen that the existence of this condition is because the work activities carried out are demands that must be carried out by the subject so that the longer the activity or the heavier the work does not make the subject fit so that more physical activity is needed outside of working time to improve the subject's fitness.[24]

Based on Global Adult Tobacco Survey: Indonesia Report 2011, currently most active smokers are aged predominantly 25-44 years old. While the result of this study showed that the majority of smokers are aged 20-29 years old due to differences of age grouping. In their 20s, or called young adulthood, individuals have freewill to do what they want and feel that they have a lot of time. This is one of the factors that influence the number of individuals who smoke at this age.[25]

The subjects of this study showed a variety of daily smoking consumption, from 1 to 24 cigarettes, with an average of 9.7 cigarettes per day. Based on the duration, majority of the subjects had been active smoker for 5-10 years (34.8%) with the overall subjects' average of 13 years. With an average duration of 13 years and 10 cigarettes per day, the Brinkman Index (BI) of the subject fell into the mild category.

This study included no smokers with severe BI, therefore, the group was excluded. This could be due to age, it is worth noting the oldest subject in this study was 57 years old. With an average of 9.7 cigarettes per day, it would take approximately 60 years of smoking to fall into the severe BI category.

The predicted values in this research was calculated using Nury's formula of the 6-minute walk test of Indonesia's population (Mongoloids). Based on Nury's study, the average values of male and female were 581.98 metres and 516.80 metres respectively.[15] Even though the subjects in this study were also Indonesian, the average value was found to be different, which were 350.92 meters for male and 336.44 metres for female. According to the American Thoracic Society (ATS), there is no global standard for the 6-minute walking distance interpretation in single measurement, therefore, Nury's study could be considered as the initial observation which can be further developed.

Based on international multicentre research, variation in geography can also affect the outcome of the 6-minute walk test, which cannot be explained by anthropometry. Furthermore, other factors such as walking habits, lifestyle, subjects' and researchers' motivations, mood, and behavior can also have an impact on the test results.[14,26] Despite standardized 6MWT instructions, the 6-minute walk test can still be influenced by the subject's speed in walking and motivation. Age, gender, height, and VEP_1 are also known to have an impact on the results.[27]

Some factors associated with lower walking test results included shorter height, older age, obesity, female gender, cognitive impairment, respiratory diseases (COPD, asthma, cystic fibrosis), cardiovascular diseases (angina, myocardium infarct, chronic heart failure, stroke), and musculoskeletal disease (arthritis). Factors known to be associated with higher 6-minute walking test results were taller height, male gender, and high motivation.[21]

The subject characteristics based on fitness level, which was further separated per gender and age, are shown in Table 3. Only one subject fell into the normal fitness level, a 23 years old male smoker with a mild BI category and a 6-minute walk test result of 491.76 metres. Previous studies had shown the male gender's association with higher 6-minute walk test results. The male gender is thought to have higher fitness due to several factors such as taller body height, footsteps, and muscle mass which enable farther mileage.

A very bad fitness level tends to increase with age. Among the subjects aged <20 years old, only two subjects (66.7%) were within the very bad fitness level category, 17 subjects aged 20-29 years old (89.4%), 22 subjects aged 30-39 years old (100%), 34 subjects aged 40-49 years old (100%), and 24 subjects from the 50-59 years old age group (96%). An increase of age is associated with a decline in organ function such as pulmonary, cardiac, and musculoskeletal function

which are known to influence the 6-minute walk test. This was also supported by the results of the study in which very bad fitness level were found more prevalent in older age groups.

The Kruskal-Wallis test using SPSS conducted in this study showed no significant relationship between smoking intensity with an individual's fitness level, which was measured using the 6-minute walk test (P=0.681). This research included subjects within the same professional group, namely janitors, with equal amount of physical activities on a daily basis required in the work.

Physical activity has a positive impact on individual health. A study conducted in Tunisia showed routine physical activity was associated with better pulmonary function, lung capacity, and physical fitness. Physical activity was also associated with an increase in VO_{2max} in various age group. The study showed that after 12 weeks of regular intermittent exercise, an increase in the parameter for pulmonary function was seen. The increase was higher in the smokers group compared to the non-smokers. Intermittent exercise could hinder the decline in respiratory function caused by smoking which could then increase the smoking group's quality of life. Individuals with higher physical activity also tend to have higher fitness level due to the increase in cardiorespiratory function.[28]

The study mentioned above supports the conclusion that janitors of UI Depok, who were the subjects of this research, had a profession requiring daily physical activities categorized as regular physical activity which could lower the risks for cardiopulmonary diseases. This may have caused the 6-minute walk test results showed no difference between smoking and non-smoking subjects.

Another factor possibly playing a part in this study was the subjects' age. The negative effects of smoking are cumulative and will add up for as long as the person smokes, affecting the musculoskeletal system, workout capacity, and health status. A study conducted in Croatia showed a difference in the Health-related Quality of Life (HRQoL) of male smokers aged >65 years old, who showed significantly worse health status compared to non-smokers of the same age range. However, subjects aged <65 years old did not show any significant difference in health compared to non-smokers. This finding suggested that within productive age, smoking hadn't shown negative impact on physical fitness yet, but did have an observable impact in subjects aged >65 years old. Another research suggested the cumulative side effects of long-term smoking started appearing in the fourth decade of an individual's life.[29]

These studies supported the idea that cumulative side effects of smoking on someone's health would most likely appear above 65 years of age. However, there could still be unpredicted variations in each individual, which would affect the timing of the impact smoking has on someone's health, largely influenced by a person's characteristics. The oldest subject of this study was aged 55 years old and showed

no signs or clinical symptoms of any diseases associated with smoking. According to the age factor, in alignment with previous studies discussed above, the subject most likely has not reached the age for peak negative side effects of smoking, therefore showing no signs or symptoms.

Cigarettes contain a number of substances harmful to normal respiratory function. Carbon monoxide (CO) in cigarettes can alter the binding of oxygen (O_2) which will then lower the aerobic peak capacity and the maximum O_2 uptake (VO_2max). CO binds to Hb and lowers the arterial oxygen saturation. Moreover, CO will also bind to myoglobin. CO will cause a decrease in VO_2max, functional capacity, and functions of the circulatory system. During exercise, hypoxemia will be more prominent.[13]

However, in this study, almost all of the subjects showed normal oxygen saturation with no signs or complaints of dyspnea suggesting no impact on the functional exercise capacity. This was also the reason for the lack of significant difference in results between smokers and non-smokers found in this research.[13]

The 6-minute walk test is one of the simple tests to show the respiratory functional capacities of individuals with cardiorespiratory impairments.[14] The subjects in these studies had no cardiorespiratory impairments, thus showed no significant difference in fitness level measured using the simple test. The 6-minute walk test, however, is a nonspecific and nondiagnostic tool. Another tool is highly recommended for further measurement of smokers' subclinical cardiorespiratory function.

CONCLUSION

Our research shows that the relationship between nutritional status, type of work, smoking activity, as well as routine and level of physical activity with fitness level measured using the 6-minute walk test method is not statistically significant. However, several factors that need to be considered such as clinical symptoms of cardiorespiratory disorders, duration and number of cigarette consumption, age, and physical activity in our study subjects can cause results that are not meaningful. So, we still recommend to maintain daily physical activity and exercise and also cease smoking before the signs and symptoms of cardiorespiratory.

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Literature Review

Optimal Intensity of Aerobic Exercise Training for Patient With Chronic Obstructive Pulmonary Disease (COPD): Systematic Review and Meta-Analysis

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Abstract

Background: Intensity for aerobic exercise is unclear in patient with COPD. Previous systematic review comparing effects of different levels of training intensity was done in 2011 and did not reach any conclusion. We conducted this systematic review to see the differences in aerobic training intensity on various aspects of health in COPD patients with updated information.

Method: We included RCTs, comparing the differences in intensity of aerobic training between groups. The primary search was done through Pubmed, Scopus, Science Direct, Proquest, and PEdro. The PEdro scale and Risk of Bias 2 tool was used to rate the studies. Lastly, we also rate the certainty of evidence using GRADE approach. The assessment was carried out by two reviewers independently. Data were extracted by one reviewer then evaluated by second reviewer.

Results: We found and analysed data from four studies with total of 472 patients. The primary outcomes extracted were Disease-specific Health-Related Quality of Life (HRQoL), Activities of Daily Living (ADL), Functional exercise capacity, Dyspnea symptoms. There was a significant difference only in St George's Respiratory Questionnaire (SGRQ) symptoms domain for HRQoL outcome (MD=5.53; 95% CI=1.08-9.97), favoured lower intensity group. No other significant results were found for any other outcomes/ outcome measures. According to GRADE, quality of the studies was very low to moderate.

Conclusion: The evidence we collected is very limited and difficult to evaluate. Further research comparing higher intensity with lower intensity of aerobic training is needed.

Keywords: chronic obstructive pulmonary disease; rehabilitation; exercise intensity; aerobic exercise

INTRODUCTION

Pulmonary rehabilitation (PR) is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies designed to improve the physical and psychological condition of people with chronic respiratory disease and promote long-term adherence to health-enhancing behaviours.[1]

Exercise, which is the cornerstone of PR, is the best way to improve muscle function in chronic obstructive pulmonary

disease (COPD).[1] Certain levels of exercise result in less lactic acid release, leading to lowered ventilation and reduced dynamic hyperinflation[2]. In addition, exercise also has positive effects such as increased motivation during exercise, reduced mood disorders, reduced severity of symptoms, improved cardiovascular function, and quality of life.[1,3] Unfortunately, the exercise program features in PR for COPD patients have not been studied much.[4] In addition, many components of PR require further research, including ideal duration and location, level of supervision, frequency and intensity of training required, and how long the effects of treatment last.[5]

Currently, there is no consensus on the optimal intensity for aerobic training in people with COPD. Some guidelines suggest high intensity >60% peak work rate[1,6] and 60-80% peak work rate.[4] However, a previous systematic review has not reached any conclusions,[7] and to our knowledge, there have not been any updates ever since.

Therefore, we conducted this systematic review to analyze the differences of aerobic training intensity on various aspects of health in COPD patients with the updated information available. This review will focus on exercise-based intervention so we will not exclude studies that did not include education and psychosocial support component.

METHOD

The analysis and inclusion criteria were predetermined and documented in PROSPERO (ID: CRD42021247904).

The established inclusion and exclusion criteria are population of patients diagnosed with COPD defined by post-bronchodilator spirometry ratio of Forced expiratory volume in first second to forced vital capacity (FEV_1/FVC) <0.70 and %FEV_1 <0.80 who undergoes aerobic training.

The studies included are studies with the intervention of 12 sessions or more, which compared differences in intensity (with same mode (cycling/walking), same frequency, continuous, with same/different volume) consistent with previous review.[7] However, a flexible approach was used to prescribe intensity with expectation to gather more evidence comparing the differences of %peak working rate (%Wmax), %maximal oxygen uptake (%VO_2max), VO_2Reserve (%VO_2R), %Heart Rate Reserve (%HRR), %Maximum Heart Rate (%HRmax) between higher and lower intensities. The intensity used for incremental training type is its highest value. This study excluded studies that compares exercise training groups with no training groups and interval exercise.

The outcomes consists of primary outcomes (disease-specific health-related quality of life (HRQoL); Activities of Daily Living (ADL); functional exercise capacity; dyspnea symptoms) and secondary outcomes (peak exercise; isowork or isotime; endurance time of the exercise test with constant work rate; and muscle strength). This study uses primary outcome as inclusion criteria. Design of study that is the inclusion criterion is only randomised

controlled trials (RCTs) in English were included with no restrictions on the type of setting.

This systematic review was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[8] The search for articles was carried out through five electronic databases: Pubmed, Scopus, Science Direct, Proquest, and PEdro. Databases search the from beginning to February 2021. Also carried out additional searches on www.clinicaltrials.gov, the WHO ICTRP portal (www.who.int/ictrp/en/), and hands-on search of identified study reference lists and journals related to respiratory medicine. According to each electronic database, the search was compiled using boolean operations, which can be seen in the supplementary file.

One reviewer (CJI) screened each article based on inclusion criteria and determined its appropriateness to be included in the study, and evaluated by the second reviewer (AP). The selection process is reported in PRISMA flow diagram. Any disagreements were resolved by discussion between relevant reviewers, with a third reviewer (AP) consulted to arbitrate if necessary.

All data extraction was done by one reviewer (CJI). The second reviewer (AP) evaluated the extracted data, disagreements in extracted data collection were resolved by discussion. The third reviewer (YSS) was consulted to arbitrate where necessary. Data extraction included characteristics of the study (study design, inclusion criteria, number of samples, disease severity) and program components (Table 1).

Assessment of the quality of the studies was carried out by two reviewers (CJI and RA) independently. Any disagreements were resolved by discussion between relevant reviewers, and a third reviewer (AP) consulted to arbitrate where necessary. The PEdro scale was used to rate each study included.[9] The scale is a valid measure of the methodological quality of clinical trials.[10]

Risk of bias assessment was conducted using the 2nd version of the Cochrane tool to assess bias risk in randomised trials (RoB 2). This instrument provides a framework for evaluating the risk of bias of all types of RCT studies and an assessment specific for each trial outcome, that is, the relative effect of the two interventions.

We extracted the mean (the change score before and after the intervention) and the standard deviation of each measured outcome. We also confronted results obtained with the established MID. The unit equalisation from % VO_2max to Wmax performed using the formula % VO_2max=12.1+0.866 (%Wmax).[11]

The following are some of the MIDs that was used for the outcome of this study:

a. St George's Respiratory Questionnaire (SGRQ): -4 points of SGRQ total score.[12]
b. Chronic Respiratory Disease Questionnaire (CRQ): 0.5 points per item, so if we calculate per domain: dyspnea (5 items): 2.5 points, fatigue

(4 items): 2 points, emotional function (7 items): 3.5 points, mastery (4 items): 2 points.[13]

c. London Chest Activity of Daily Living scale (LCADL): 3 points.[14]
d. Six-Minute Walk Test (6MWT): Median 30 meters (25-33 meters).[15]
e. Modified Medical Research Council (mMRC) dyspnea scale: 1 unit.[16]
f. Mahler's Transition Dyspnea Index (TDI): 1 unit.[17]
g. Cycle endurance: 1.68 minutes (95% CI=1.43-1.93).[18]

The study was grouped per outcome measure. The meta-analysis used a forest plot, inverse variance statistical method, random-effect analysis model, and 95% Confidence Interval (CI) using Review Manager (Revman) 5.4.1 application[19].

To address missing data, we contacted the authors of the relevant studies. When the change score is not shown in the study, we calculated with these listed methods:

a. If the mean after intervention and baseline are available, Mean change score = $\text{Mean}_{\text{post}} - \text{Mean}_{\text{baseline}}$
b. If the mean score from the baseline and/or post-intervention is not available, We used data such as the median or the mean imputation from another similar study
c. If the standard deviation is not displayed, SD of mean change = $\sqrt{((\text{SD}^2\text{post} + \text{SD}^2\text{baseline})/2)}$,[20] or transform the data using CI and Standard Error, or impute the data from other studies.[21]

We examined statistical heterogeneity using the chi-squared test (Cochran's Q) dan I^2 test with P=0.10. I^2 test describes the percentage of variability in effect estimates due to heterogeneity rather than chance alone. Following are the I^2 test cutoffs that were used in this review:[22]

a. 0% to 40%: might not be important;
b. 30% to 60%: may represent moderate heterogeneity;
c. 50% to 90%: may represent substantial heterogeneity;
d. 75% to 100%: considerable heterogeneity.

As all meta-analyses included fewer than ten studies, we did not create the funnel plot because it can be very problematic when the number of studies is small, in which case they can appear spuriously wide or spuriously narrow.[22]

The quality of evidence was assessed using the GRADEpro Guideline Development Tool software.[23] We created a "Summary of findings" table using the seven most important outcomes. Finally, we justified all decisions to derive the quality of the evidence using footnotes and comments if needed.

Sensitivity analysis is performed on the important outcomes listed in the Summary of Findings table, which can be seen in the supplementary file. In this review this analysis performed if these one of these conditions are met:

a. High risk of bias
b. The intensity in the intervention/control group is only an estimate

c. Substantial methodological heterogeneity

Subgroup analysis can be performed to investigate mixed results or answer specific questions about a particular patient group, type of intervention, or type of study.[22] In this review, the analysis was carried out as the difference in work volume per session. The work volume of the session is an essential determinant of training response and is often calculated as the intensity multiplied by the duration of the exercise.

RESULTS

From the search results of five primary databases, we found 6039 articles, 414 articles from Pubmed, 2509 articles from Proquest, 2407 articles from Scopus, 963 articles from ScienceDirect, 45 articles from the PEDro database, and five articles from hands-on search. After eliminating the duplicates, 5091 remaining articles went through title and abstract screening. We excluded 5042 articles that were not an RCT study/irrelevant to the topic discussed. Of the remaining 36 articles, a full-text screening was carried out, where 32 articles were excluded for several reasons, which can be seen in a schematic diagram illustrating this process (Figure 1).

There were four studies with 472 patients whose data were synthesised, with 404 included in primary analyses suffering from moderate-severe COPD, 204 of whom received higher-intensity interventions, and 200 others received lower-intensity interventions[24–27]. Two studies compared the intensity of 80% Wmax with 60% Wmax[25,26], one study compared 80% Wmax with 50% Wmax[24], and one study compared >70% VO2max (>72.7% Wmax) with 50-70% VO2max (55.4%-72.7% Wmax)[27]. A complete description of each study can be seen in Table 1.

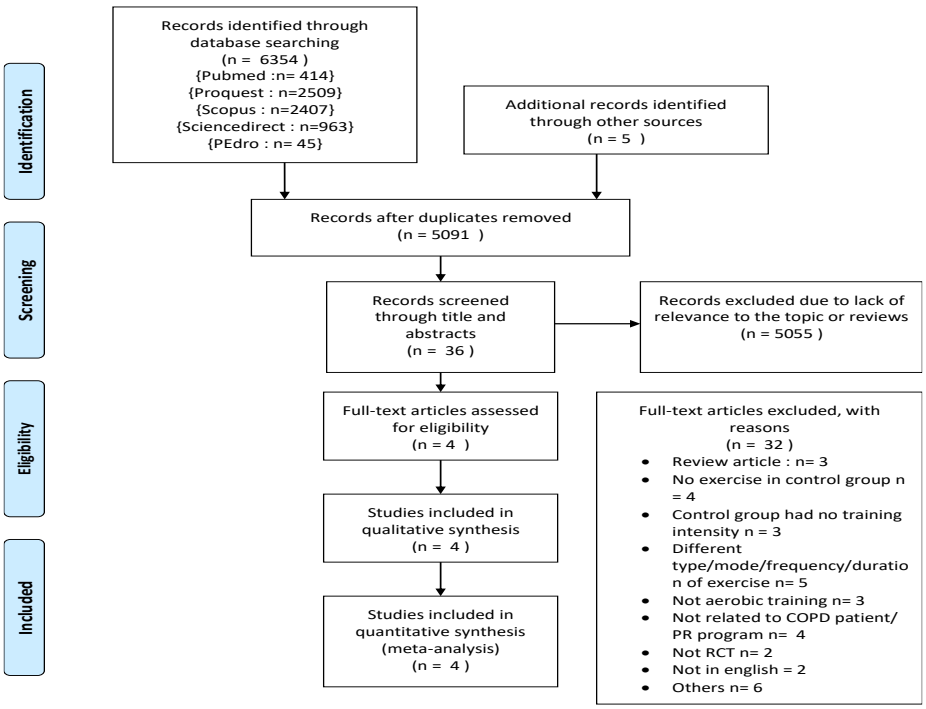

Figure 1. Flowchart of Literature Search and Study Selection

Table 1. Study Characteristics

Study	Participants	Setting, Frequency, Length	High Intensity(HI)	Low intensity(LI)	Outcomes	Withdrawals	Comments
Casaburi et al[24] (RCT)	Total: 34 patients(17 patients each group) with COPD (mean age 52 y; FEV_1 56% predicted)	Outpatient, five days/week for eight weeks	Continuous constant cycle ergometry at 60% difference between anaerobic threshold(AT) and VO_2 max work rate / 80% Wmax, 45 minutes/ session	Continuous constant cycle ergometry at 90% AT and VO_2 max work rate/ 50% peak work rate, 72 minutes/ sessions	Endurance, Lactate threshold	-	-
Maltais et al[25] (RCT)	Total: 252 patients (126 patients each group) with COPD (mean age 66y; FEV_1 45% predicted)	Higher intensity: outpatient Lower intensity: home Three days/week for eight weeks	Continuous constant cycle ergometry at 80% Wmax for 25-30 minutes	Continuous constant cycle ergometry at 60% Wmax for 40 minutes	CRQ, SGRQ, 6MWD, Endurance	36 patients 17 in HI group: 14 withdrew, two lost to follow up, one died 19 in LI group: 16 withdrew, two lost to follow up, one died	Additional strength training for 30 minutes per session
Santos et al[26] (RCT)	Total: 34 patients (17 patients each group) with COPD (mean age 67y; FEV_1 55% predicted)	Outpatient, 3 days/week for 8 weeks (atleast 20 sessions)	Continuous (94%)/interval (6%) threadmill (74%)/ cycle (24%) ergometry at 80% Wmax for 30 minutes per session	Continuous (94%)/interval (6%) threadmill (74%)/ cycle (24%) ergometry at 60% Wmax for 30 minutes per session	SGRQ, LCADL, TDI, 6MWD, Peak exercise capacity, Endurance	Six patients: loss to follow up (2 in HI group 4 in LI group)	Additional strength training for two days/weeks, flexibility training three days/weeks, and five educational skills training
He et al[27] (RCT)	Total: 217 patients (73 patients each for high and moderate intensity group), 71 patients for low intensity group) with COPD (mean age 65y; FEV_1 48% predicted)	Outpatient, 5days/week for 20 weeks	Continuous incremental cycling starting at 50% W peak progressively increased by 10W until >70% VO_2max reached for 20 minutes per session	Continuous incremental cycling starting at 50% W peak progressively increased by 10W until 50-70% VO_2max reached for 20 minutes per session (moderate-intensity group)	mMRC, 6MWD	14 patients(6 in HI group, 5 in moderate intensity group, 3 in low intensity group) HI: three poor cooperation Moderate: four poor cooperation, one death with AE	Three-arm study, the low intensity group used in the primary analysis in our review is the moderate intensity group in the trial, Low-intensity group: Continuous incremental

Study	Participants	Setting, Frequency, Length	High Intensity(HI)	Low intensity(LI)	Outcomes	Withdrawals	Comments
						Low intensity: five poor cooperation, one death with AE	cycling starting at 50% W peak progressively increased by 10W until <50% VO_2max reached for 20 minutes per session (low-intensity group) Additional ten minutes of warm-up before training and ten minutes of relaxation after training, ten education session in all the groups

The sensitivity test was carried out in the study by He et al due to the intensity level used is only an estimation.[27] We also removed the study by Maltais et al due to differences in supervision between groups.[25] Subgroup analysis was performed by dividing the studies into two groups. The first group compared intensity with different exercise volumes (duration x intensity), while the second group compared intensity with the same exercise volume.

The risk of bias within included studies and across studies assessed with the assessment of study quality based on the PEdro scale can be seen in Table 2. The average score obtained was 6.5, with a score range of 6-7. The evaluation of each outcome using the RoB2 tools can be seen in Figure 2.

For the intervention effect, we did not analyse the results on several outcomes, including isowork, isotime, and peak exercise, because no new studies discuss these outcomes in relation to the last systematic review.[7] We also did not analyse muscle strength outcomes because no studies addressed this topic.

1. HRQoL

This assessment uses two different questionnaires (SGRQ and CRQ). Two studies reported HRQoL using the SGRQ questionnaire, where 112 patients were trained at a higher intensity and 106 patients at a lower intensity.[25,26]

On the SGRQ, higher scores indicate poorer quality of life; therefore, a positive effect favours the lower-intensity group.

Table 2. Quality Assessment Using the PEdro Scale

Study	Random allocation	Concealed allocation	Similarity at baseline	Subject blinding	Therapist blinding	Assessor blinding	Completeness of follow up	Intention-to-treat analysis	Between-group statistical comparison	Variability estimates	Total
Casaburi et al[24]	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Maltais et al[25]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Santos et al[26]	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	6
He et al[27]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	7

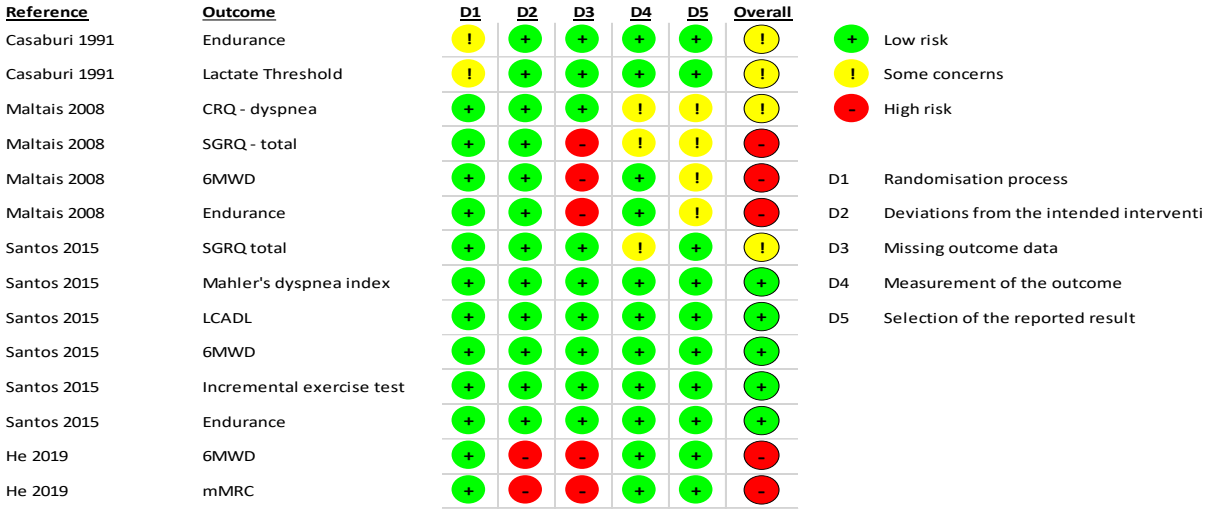

Figure 2. Risk of Bias Assessment using Version 2 of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2)

There was a significant difference in symptoms domain (MD=5.53; 95% CI=1.08-9.97), favouring the lower-intensity group (Supplementary Figure S1). The common effect size exceeds the MID limit of 4 points, but the lower limit of the confidence interval does not exceed the MID. The total score (MD=1.79; 95% CI= -0.90 - 4.48; Low quality evidence), activity domain (MD=1.77; 95% CI= -3.51 - 7.05) and impact domain (MD=0.60 ; 95% CI= -2.52 - 3.71) on the SGRQ also favored the lower intensity, but there was no significant difference (Supplementary Figure S2-4). There was no heterogeneity in all domains, except in the activity domain (I^2 test = 27%), which suggests that the existing heterogeneity may not be important. Subgroup analysis showed no significant differences between subgroups (based on exercise volume) from all domains and total scores.

One study reported HRQoL using the CRQ questionnaire in which the total number of patients in the higher-intensity group was 109 people, and the lower intensity was 107.[25] On CRQ, higher scores indicate better quality of life; therefore, positive effect favours higher intensity group. There were no significant differences in all CRQ domains between the two groups (dyspnea (MD= -0.04; 95% CI= -0.30 - 0.22; Low quality evidence), mastery (MD=0.02; 95% CI= -0.21 - 0.25), fatigue (MD=0.10;95% CI= -0.17 - 0.37),

emotion (MD=0.03; 95% CI= -0.18 - 0.24) (Supplementary Figure S5-8).

2. Activities of Daily Living

ADL was only reported in one study where the total number of patients at a higher intensity and a lower intensity each of 17 people.[26] In LCADL, higher scores indicate poorer quality of life; therefore positive score favours the lower-intensity group. The effect obtained favoured lower intensity, but there was no significant difference between the two groups (MD=0.8; 95% CI= -1.24 - 1.84; Moderate quality evidence) (Supplementary Figure S9).

3. Functional exercise capacity

Comparison of functional exercise capacity was assessed by three studies using the 6MWT test.[25–27] The total number of participants was 179 people in the higher-intensity group and 174 people in the lower-intensity group. The effect favours higher intensity, but there were no significant differences (MD=6.20; 95% CI= -4.80 - 17.20; Very low quality of evidence) (Supplementary S10). Heterogeneity was not found in either the chi-squared test (P=0.54) or the I^2 test (0%).

We performed a secondary analysis on the study by He et al because there were three different groups.[27] This analysis compares a high-intensity (>70% VO_2max) group with a low intensity (<50% VO_2max) group (Supplementary Figure S19). The effect favours the high-intensity group where significant results were obtained (MD=28.60; 95% CI=4.82-52.38), and the effect crossed the MID limit. However, the lower limit of the confidence interval does not exceed the MID limit. The second analysis compared the moderate intensity (50-70% VO_2max) with the low-intensity group (<50% VO_2max) (Supplementary Figure S20). The effect obtained was favourable to moderate intensity but showed no significant results (MD=11.50; 95% CI= -11.20 - 34.20).

4. Dyspnea symptom

There were a total of two studies comparing dyspnea symptoms in patients with higher and lower intensity, each using a different questionnaire (mMRC and Mahler's dyspnea index).[26,27] mMRC is used to evaluate the intensity of dyspnea in daily activities. One study reported dyspnea symptoms using mMRC, where the total number of patients at the higher intensity was 67 people, and at the lower intensity was 68 people.[27] A higher score indicates more severe dyspnea symptoms; therefore positive score favours the lower-intensity group. Effect favours the higher intensity groups, but no significant differences were found (MD= -0.30; 95% CI= -0.73 - 0.13; Low-quality evidence) (Supplementary Figure S11).

We performed two secondary analyses on the study by He et al because there were three different groups[27]. The first analysis compares the highest intensity (>70% VO_2max) group with the lowest intensity (<50% VO_2max) group (Supplementary Figure S21). The effect favours the high-intensity group, and there were significant differences between

groups (MD= -0.60; 95% CI= -0.87 – -0.33) but did not exceed the MID threshold. Another analysis compared the moderate intensity (50% -70% VO_2max) with the low-intensity group (<50% VO_2max), where the effect favours moderate-intensity groups, but there were no significant differences (MD= -0.30; 95% CI= -0.73 - 0.13) (Supplementary Figure S22).

One study assessed dyspnea symptoms using the Mahler's Transitional Dyspnea Index (TDI) instrument.[26] Higher scores indicate less severe dyspnea symptoms; therefore, a positive effect favours the higher-intensity group. Effect favours higher intensity groups but showed no significant differences (MD=0.50; 95% CI= -1.63 - 2.63; Moderate quality evidence) (Supplementary Figure S12).

5. Endurance

There were a total of 3 studies comparing endurance in patients with higher and lower intensity exercise.[24–26] The total number of patients at the higher intensity was 123 people, and at the lower intensity was 114 people. Effect favours the higher intensity groups but showed no significant differences (MD=1.22; 95% CI= -1.61 - 4,05; Very low quality of evidence) (Supplementary Figure S13). Heterogeneity between studies was found from the chi-squared test results (P=0.03) dan 70% in the I^2 test, which showed the possibility of substantial heterogeneity. There was no significant heterogeneity between subgroups based on exercise volume, but there was significant heterogeneity in the subgroup with the same training volume (chi-squared test P=0.01; I^2 test = 84%). We also performed a secondary analysis on the study by Casaburi et al, which used the anaerobic threshold as a boundary in choosing the work rate[24] (Supplementary Figure S23). A significant effect was found (MD=4.20; 95% CI=1.30-7.10), favouring intensity above the anaerobic threshold.

6. Peak exercise

Two studies assessed a comparison of peak exercise.[24,26] One study measured peak aerobic capacity, where the total number of patients at higher and lower intensities was 17 each.[26] The effect favours higher intensity but showed no significant difference (MD=0.40; 95% CI= -0.28 - 1.08) (Supplementary Figure S14).

One other study measured comparison of the lactate threshold on the incremental exercise test.[24] The total number of patients at higher intensity was 11 people, and at lower intensity was eight people. A higher lactate threshold indicates better exercise tolerance. The effect favours higher intensity but showed no significant difference (MD=0.10; 95% CI= -0.02 - 0.22) (Supplementary Figure S15).

7. Sensitivity analysis

We removed two studies in the sensitivity analysis.[25,27] We excluded the study by Maltais et al because it had a high risk of bias and differences in supervision which could become a confounding variable.[25] Meanwhile, the study by He et al was excluded because of the high risk of

bias, and the intensity used was only an estimation.[27]

The sensitivity analysis of the SGRQ total score omits the study from Maltais et al,[25] leaving only the study by Santos et al[26] (Supplementary Figure S16). Effect favours lower-intensity group, but showed no significant difference between the two groups (MD=4.10; 95% CI= -3.01 - 11.21), which is consistent with the primary analysis. In the sensitivity analysis of 6MWT, we removed the study by He et al and Maltais et al,[25,27] leaving only Santos et al.[26]

The effect favours the lower-intensity group, but there was no significant difference (MD= -3.50; 95% CI= -64.32 - 57.32) (Supplementary Figure S17). In the endurance test sensitivity analysis, we removed the study by Maltais et al,[25] leaving two studies by Casaburi et al and Santos et al.[24,26] (Supplementary Figure S18). The pooled effect favours lower intensity, but the difference is not significant (P=0.35), and there was substantial heterogeneity (I^2 test = 72%). The differences between subgroups were significant (P=0.06) with the I^2 test = 72.3%

DISCUSSION

This review aims to describe the available evidence for interventions that compare aerobic exercise intensity in COPD patients. Previous systematic reviews and meta-analyses comparing the intensity of PR were done in 2011.[7] The criteria used are more flexible, comparing the difference between %peak working rate (%Wmax), %maximal oxygen uptake (%VO_2max), %VO_2Reserve (%VO_2R), %Heart Rate Reserve (%HRR), and %Maximum Heart Rate (%HRmax) between higher and lower intensities. The calculated intensity is the highest number, so studies using incremental training can be compared with constant training. We used these criteria due to the lack of evidence found in the previous review. One new study was included,[27] and a study from Santos et al, which was referred to in this study, showed slight data differences from the last review because the article had not been published.[26]

The primary analysis results using HRQoL tools (SGRQ and CRQ) showed a beneficial effect at lower intensities. However, the differences were not significant, except for the symptoms domain of the SGRQ instrument. However, these results are unclear because the confounding variables from the study of Maltais et al may affect the pooled effect.[25]

In this study, the group with higher intensity undertook an outpatient program at the hospital and received direct supervision. The group with lower intensity was put in a self-monitored rehabilitation program at home so that there was a possibility of inadequate supervision. The sensitivity analysis was carried out on the SGRQ total score leaving only one small study,[26] favouring the lower-intensity group but showed no significant result. The ADL outcome also favoured a lower intensity in the primary analysis, but no significant effect was found.[26] The results

of this analysis should be interpreted with caution because there were only 17 people in each group.

The 6MWT is often used to perform functional capacity assessments in COPD because of its simplicity. There were three studies comparing 6MWT between higher and lower intensities.[25–27] The pooled effect favoured higher intensity but showed no significant difference between the two groups. Similar to HRQoL, the largest proportion of this pooled effect comes from the study of Maltais et al, where the effects obtained are possibly unclear due to differences in supervision.[25]

In addition, most of the patients exercised by cycling were different from the outcome test, where patients exercised by walking according to the 6MWT method. Therefore, the effect may not be accurate. Finally, the sensitivity analysis performed on a small study favoured lower-intensity but not significant[26].

Dyspnea is one of the most prominent symptoms in COPD patients.[1,4,28] Tools for measuring dyspnea are divided into three main categories: short-term intensity measurements, situational measurements, and the measurement of the impact of dyspnea. There are two questionnaires obtained from the included studies in measuring dyspnea, namely Modified British Medical Research Council Questionnaire (mMRC) and transition dyspnea index (TDI). Both are situational measurements that quantify dyspnea. In addition, two other tools measure dyspnea in this review, namely the dyspnea domain of CRQ and the dyspnea domain of SGRQ, which measures the impact of dyspnea, but both are discussed in the outcome quality of life. The pooled effect in the primary analysis of the two tools favours higher intensity, but this effect is not significant. However, these results are still unclear because each questionnaire was only reported by one study.[26,27]

In three studies that carried out the endurance test, subjects performed the test according to their training mode. The therapeutic effect favoured higher intensity but insignificant with substantial heterogeneity. Substantial heterogeneity could also be found in the subgroups with the same exercise volume. Heterogeneity may be due to the study by Casaburi et al,[24] which used lactate threshold as the basis for the prescription while Maltais et al did not.[25]

When a sensitivity test was performed, omitting the study by Maltais et al,[25] substantial heterogeneity between subgroups by volume was found. However, it seems the heterogeneity is not due to the difference in volume because the effect shown in the subgroups with different volumes of work favoured the lower-intensity group. Instead, this may be due to the study by Casaburi et al,[24] which used the lactate threshold as the basis for the prescription. Further research is needed to conclude this effect, as the two studies we used showed opposite effects.

In peak exercise capacity assessment, the effect is also unclear because only two studies were included.[24,26] Two different outcome tests were used: peak aerobic capacity and

lactate threshold, each of which came from one study, and both favoured higher intensity but not significant. However, a previous analysis showed that a higher-intensity exercise program produced significantly lower lactate in iso-work and ventilation at iso-time than a low-intensity training program. These results are based on one study comparing higher intensity which induces a lactate threshold, and lower intensity which does not induce a lactate threshold.[7,24]

With all the limitations, there are no significant results between groups of higher intensity with lower intensity in this review for the patient-centred outcome, except for analysis of the SGRQ symptoms domain.

However, the secondary analysis which was carried out in the He et al study comparing high intensity (>70% VO_2max) and lowest intensity (<50% VO_2max) in the 6MWT and dyspnea, found favourable result for the high intensity and was significant. On the other hand, comparison analysis of moderate (50-70% VO_2max) and low intensity (<50% VO_2max) found favourable results for moderate-intensity but showed no significant difference.[27]

This could support a theory that in normal people, exercise at the anaerobic threshold level has a more beneficial effect than exercise below the anaerobic threshold. This seems to be also true for patients with COPD.[4,29] If we assume the lactate threshold in normal people is the same as in COPD patients (around 60% Wmax/VO_2max), then maybe comparisons made in the two studies between 80% Wmax and 60% Wmax had no significant effect because both groups trained above the lactate threshold.[25,26] Conversely, one study comparing 80% Wmax with 50% Wmax obtained significant results because the lower intensity has not crossed the lactate threshold.[24] Also, studies comparing >70% VO_2max with 50-70% VO_2max do not obtain significant results because the intensity described is only an estimate, some of which cross the lactate threshold and some do not.[27] We cannot confirm this hypothesis because the lactate threshold was not measured in these studies (except the study by Casaburi et al[24]).

Based on the studies included in this review, it was found that higher intensity is not always better, especially after 60% Wmax. However, this cannot be confirmed and requires further study.

This review has several strengths, including a more in-depth analysis and discussion than the previous review, which can be done because of the inclusion of new studies. In addition, all data used in the meta-analysis were uniformly using a change score.

The main limitation is that the evidence we had collected is scanty and difficult to evaluate, although the criteria are more flexible. In addition, we suggest carefully interpreting the data in this review because based on the assessment of evidence using GRADE, the quality of several primary outcomes was very low-moderate (the quality of the evidence is low for HRQoL, moderate for ADL, very low for exercise tolerance, low-moderate for dyspnea symptoms and very low for

endurances). The decline in the quality of evidence is primarily due to the imprecision where the sample size is too small for each meta-analysis, high risk of bias, and indirectness because there are studies with confounding variables. See the Summary of Findings to see in full the reasons for the deduction in study quality.

CONCLUSION

The evidence we collected is scanty and difficult to evaluate. This review is still inconclusive and indicates there is still a gap of knowledge in this topic. Further research comparing higher intensity with lower intensity of PR in COPD patients is still needed, especially studies with the same setting, mode, type, total sessions, time, and frequency so that there are no confounding variables.

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Literature Review

Gut-Lung Axis

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Abstract

Microbiota and the body's immune system have a two-way interaction that is interconnected. The microbiota plays a role in the formation and maturation of the immune system, on the other hand, the immune system shapes the composition and function of the microbiota. This interaction is important in maintaining the body's immune system's homeostasis. The human intestine contains various types of microbes that form the gut microbiota. Various studies have found that changes in the gut microbiota are associated with immunity in distal tissues such as the lung. This gives rise to the concept of a feedback relationship between the gut and lung organs called the gut-lung axis. Through this axis, changes in the composition of the gut microbiota not only cause abnormalities in the gut but also affect microbiota in the lungs and can cause disease. One of the important routes in the transmission of substances from the intestine is through the mesenteric lymphatics. Probiotics can help improve the gut's defense mechanism. A high-fiber diet can also reduce pathogenic bacteria by increasing levels of short-chain fatty acids. Therefore, a healthy lifestyle is needed to maintain the balance of the microbiota.

Keywords: gut-lung axis, immunity, microbiota

INTRODUCTION

Human organs consist of a collection of tissues that work together. The tissue contains microbes, including bacteria, viruses, fungi, and parasites that live in host cells to form a microbiota. The microbiota plays a role in the formation and maturation of the immune system. Meanwhile, the immune system forms the composition and function of the microbiota that affect the inflammatory response in the body. This interaction is essential in maintaining the homeostasis of the human immune system.[1,2] Microbes also have a mutualistic relationship with the host cell. Microbes benefit from a nutrient-rich environment, whereas microbes have a vital role in the fermentation of food components to produce nutrients, vitamins, and metabolites.[2,3]

The human gut contains more than 10^{14} cells with various bacteria that make up the gut microbiota.[3,4] Changes in the composition and function of the microbiota are called dysbiosis.[1–5] Dysbiosis can be influenced by various factors such as genetic or exogenous factors such as diet, use of antibiotics, and exposure to cigarette smoke. These conditions are associated with a decline of immune

responses that occurs in the gastrointestinal tract and other organs, including the respiratory tract.[2–6]

Alterations in the gut microbiota are associated with changes in lung immunity. On the other hand, the microbiota in the lungs also influences the microbiota in the gut. It gives rise to the concept of a feedback relationship between the gut and lung organs called the gut-lung axis. Through this axis, disease in the intestine can cause pathological lung conditions and vice versa.[1–6] This literature review aims to provide knowledge about the relationship between the intestine and the lungs through the gut-lung axis which can be useful in the management of lung disease.

GUT MICROBIOTA

Many studies have been conducted on microbes in the gastrointestinal tract, especially in the intestines. The microbiota varied along the gastrointestinal tract. Environmental pH, bile acid concentration, digestive retention time, and host defense factors influence these differences.[5]

The gastrointestinal tract is dominated by four bacterial phyla, namely *Firmicutes* (e.g., *Lactobacillus, Bacillus, Clostridium*), *Bacteroidetes* (e.g., *Bacteroides*), *Proteobacteria* (e.g., *Escherichia*) and *Actinobacteria* (e.g., *Bifidobacterium*). Some other types with fewer numbers are *Fusobacteria*, *Verrucomicrobia*, and *Spirochaeta*.[5] The number of T cells in the gut, such as CD4+ and T helper (Th) cells, including Th1, Th2, and Th17, is influenced by the microbiota in the intestinal epithelium. The gut microbiota can induce regulatory T cells (Treg) in the large intestine that regulate the immune response by increasing the production of transforming growth factor (TGF)-β.[1]

Gram-positive bacteria can translocate through dysfunctional mucus layers as in ulcerative colitis and induce an immune response. Commensal bacteria such as *Segmented filamentous bacteria* (SFB) induce the accumulation of Th17 cells in the small intestine.[5,7]

The microbiota furthermore plays a role in inducing antibody responses. Production of immunoglobulin A (IgA) occurs through the gut-associated lymphoid tissue (GALT). Through effector sites on these cells, plasma cells produce specific antibodies and form mucosal immunity. This circumstance indicates a relationship between gut microbiota and intestinal mucosal immunity.[1,2]

GUT BARRIER AND BLOOD VESSEL

The gut barrier plays a vital role in metabolic homeostasis. They regulate the absorption of water, electrolytes, and nutrients and also obstruct bacteria or harmful substances in the intestines from entering circulation. The intestinal barrier consists of three layers, namely mucus, epithelium, and endothelium, as shown in Figure 1. The mucus layer lining the lumen is a fibrous tissue comprised of protein and mucin produced by goblet cells. This layer also contains antimicrobial peptides secreted by Paneth cells and

immunoglobulin A secreted by plasma cells.[8]

The small intestine has a layer of connective tissue and mucus, while the large intestine has two layers of mucus. The epithelial layer is formed by enterocytes, goblet cells, Paneth cells, and other enteroendocrine cells, which are connected through tight junctions (TJ), adherent junctions (AJ), desmosomes, and gap junctions. Disruption of the intestinal barrier is common in critically ill patients. Adequate enteral therapy is essential in maintaining the intestinal defense system and reducing the incidence of multiorgan failure in septic and trauma patients. Inflammatory mediators such as Interferon Gamma (IFN-ɣ), Interleukin-6 (IL-6), and Tumor Necrosis Factor Alpha (TNF-α) can disrupt the TJ and increase epithelial permeability.[1,8]

In response to stress, the blood vessels in the intestines will experience vasoconstriction to maintain the blood supply to vital organs. This condition will affect the protuberances in the intestines, which are drained by an artery and are sensitive to damage. A brief ischemic period can cause local tissue damage, epithelial apoptosis, and intestinal barrier breakdown. The damaged barrier layer will become a site to spread bacteria, toxins, and other tissue products in the intestine through the barrier.[1,8]

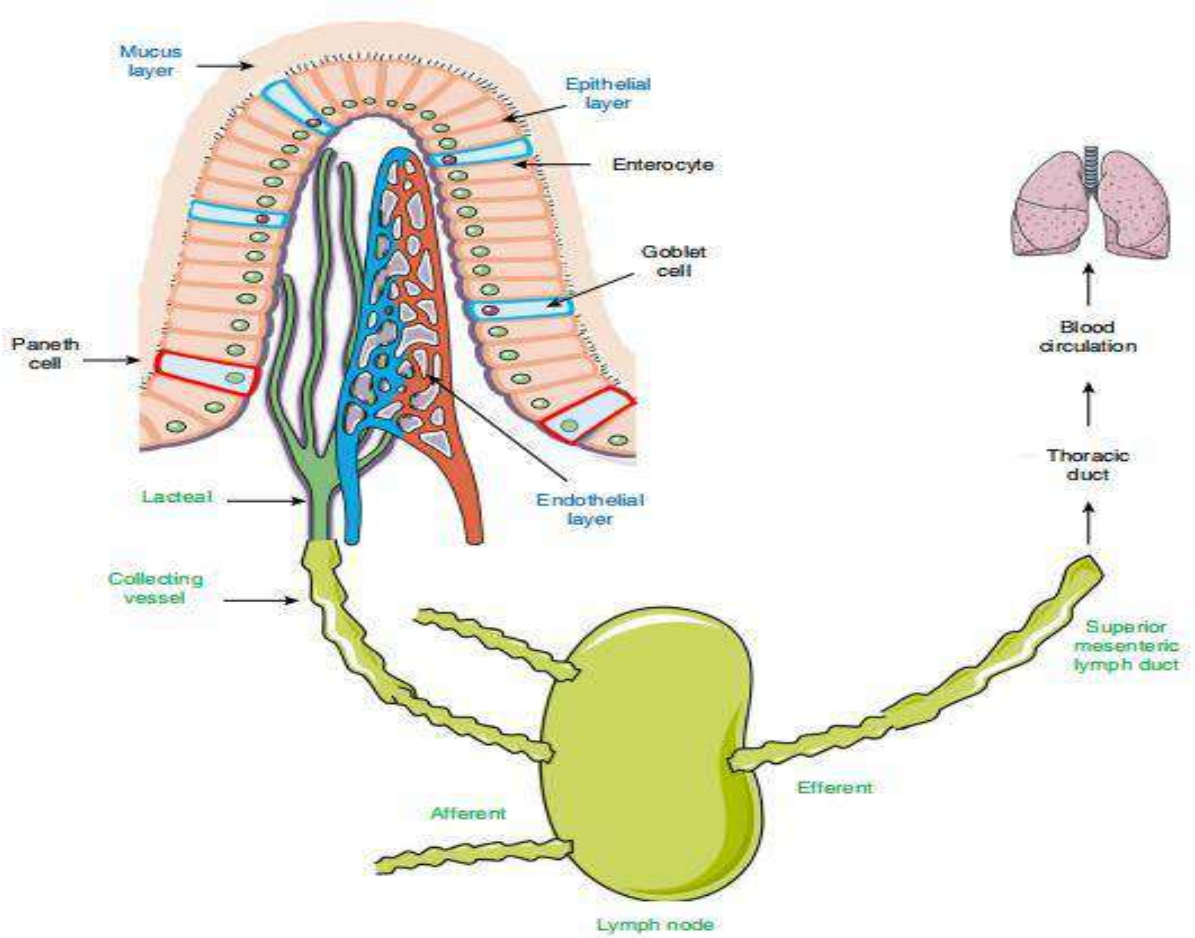
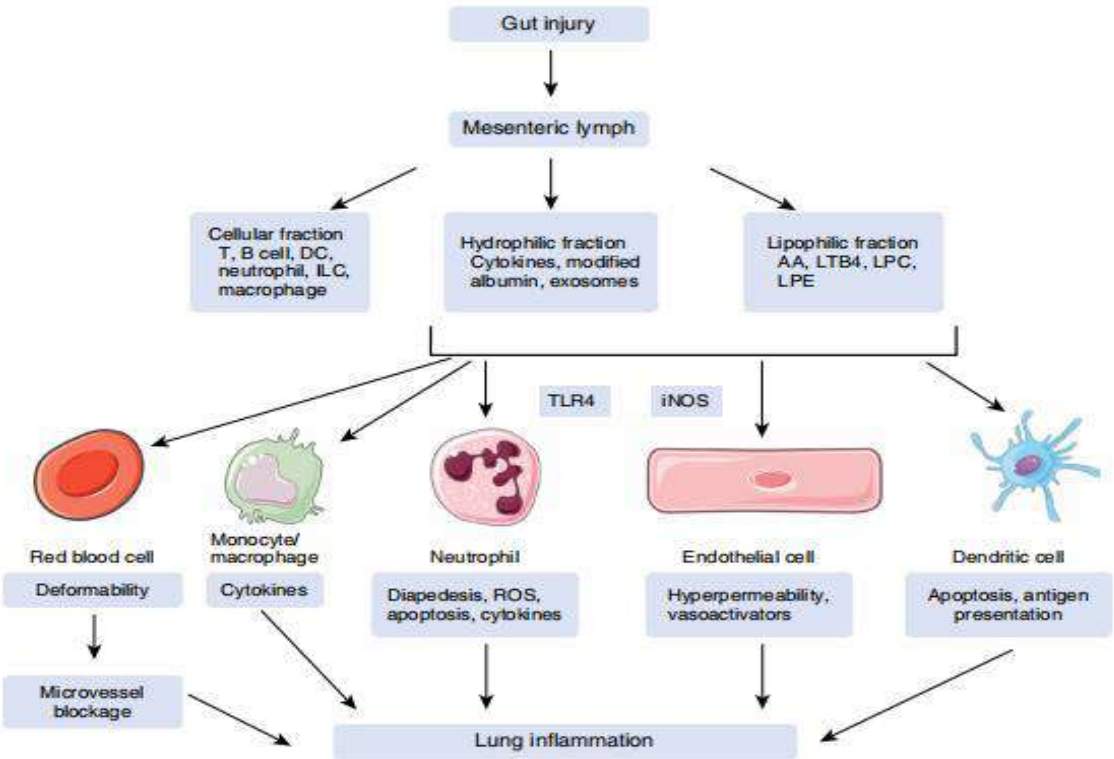


Figure 1. Intestinal barrier and lymphatic system[8]

MESENTERIC LYMPHATICS

The intestine has two drainage systems: the portal venous system and the mesenteric lymphatic system. Mesenteric lymphatic vessels are arranged to form a network called lacteals. Interstitial fluid exits the intestine into the lacteals to form lymph fluid. The fluid travels through the lymphatic vessels to the superior mesenteric lymphatic duct, the thoracic duct, or returns to the blood circulation via the subclavian vein. Under pathological conditions, neutrophils traveling to inflamed tissues may migrate to lymph nodes. Dendritic cells also exit the lamina propria into the spleen in the small intestine.[1,7,8]

In conditions of intraperitoneal infection, neutrophil levels increase in the mesenteric lymphatics and form systemic inflammation that can cause pulmonary disorders. Based on these circumstances, several studies have stated that mesenteric lymphatics are essential for spreading substances from the intestines to other organs, including the lungs. After the damage to intestinal tissue, mesenteric lymphatics lipophilic and hydrophilic components can activate endothelial cells, neutrophils, and monocytes or macrophages, as shown in Figure 2. These components induce endothelial cell barrier dysfunction, slow neutrophil apoptosis, and inhibit red blood cell deformability and dendritic cell function. These will contribute to systemic inflammation and acute lung tissue damage.[1,7,8]



Note: AA = arachidonic acid; ILC = innate lymphoid cell; iNOS = inducible nitric oxide synthase; LPC = lysophosphatidyl-choline; LPE = lysophosphatidyl-ethanolamine; LTB4 = leukotriene B4; ROS = reactive oxygen species; TLR4 = Toll-like receptor 4

Figure 2. Mechanism lung inflammation after gut injury via mesenteric lymphatic[8]

LUNG MICROBIOTA

Previous studies on lung microbiota state that normal lungs are in sterile conditions, free from microbes.[1,3–7] The Next Generation Sequencing (NGS) technique was developed with the development of science and technology. Through amplification and analysis of 16S ribosomal RNA (rRNA), there were microbes in the lungs of healthy people that formed the microbiota like in the intestines.[2,9]

The phyla in healthy people's lungs include *Bacteroidetes, Proteobacteria, Firmicutes, Actinobacteria, Fusobacteria*, and *Cyanobacteria*. The most dominant phyla are *Bacteroidetes, Firmicutes*, and *Proteobacteria*. Some dominant types of bacteria are *Pseudomonas, Streptococcus, Prevotella*, *Fusobacteria*, and *Veillonella.*[3,9]

The benefits of the lung microbiota for host cells include enhancing the function and structure of the mucosa, forming the adaptive and innate immune systems, and protecting against harmful pathogenic infections. Before birth, the body's immune system pattern is dominated by Th2 cells. After birth, pattern recognition receptors (PRR) will induce changes in Th2 to Th1, protecting against asthma and allergies in neonates. Research in mice with the administration of bacteria or their components such as lipopeptides, peptidoglycans, and lipopolysaccharides (LPS) can induce Th1 immune responses against asthma and allergies, as shown in Figure 3.[10]

In the lungs, the number of bacteria increases in the first two weeks after birth. The bacterial phylum changed from *Gammaproteobacteria* and *Firmicutes* to *Bacteroidetes*. Changes in the microbiota are related to the formation of T_{reg} cells in the lungs, reducing the incidence of allergies.[10]

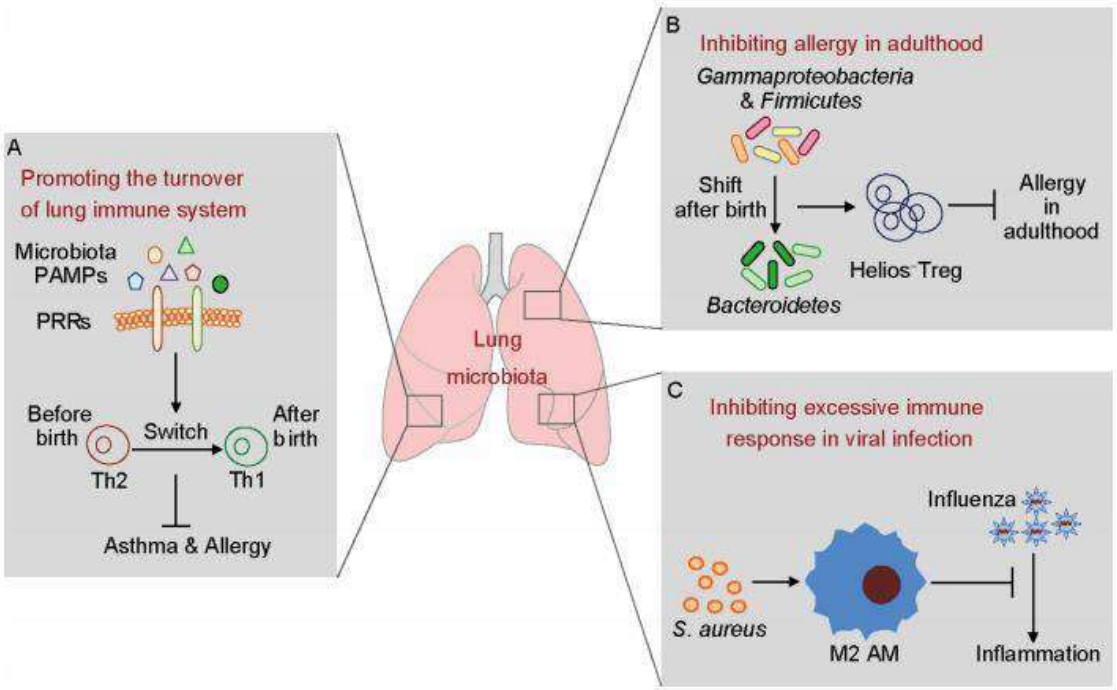


Figure 3. The function of lung microbiota in immune system[10]

Previous studies found that the microbiota in the upper respiratory tract also protects against inflammation in the lungs caused by influenza infection. *Staphylococcus aureus* colonizes the upper respiratory tract in humans increasing M2 macrophage differentiation, which significantly reduces the inflammatory response in the lung.[10]

MICROBIOTAS IN LUNG DISEASE

Asthma is a chronic and multifactorial disease caused by genetics and environmental factors such as air pollution and allergens. In asthmatic patients, *Proteobacteria* were found more, and *Bacteroidetes* were less. Research by Ege found that children who grew up in rural areas were exposed to more environmental microbes and had a lower risk of developing asthma than children who lived in cities.[10,11] Changes in the microbiota were also found in patients with severe COPD. Under these conditions, more *Proteobacteria* or *Firmicutes* were found, and *Bacteroidetes* were less, similar to asthmatic patients.[1,3]

In tuberculosis (TB), chronic infection can be latent for several years before reactivation and destroying lung tissue. Research conducted on TB patients while the patient was infected and while taking anti-tuberculosis drugs (ATD) showed that the composition of the bacteria in the gut changed and was associated with disease progression. ATD therapy can alter the gut microbiota causing a dysbiosis condition that occurs even after discontinued therapy. Long-term ATD therapy can increase the patient's susceptibility to other diseases.[6]

Research conducted by Diallo et al showed that there were changes in the gut microbiota and impaired innate immunity in patients receiving ATD therapy through decreased expression of major histocompatibility complex class II (MHC-II) and CD86. It would decrease the ability of antigen presentation and activation of dendritic cells in the lung.[6]

Other studies have also shown a decrease in the function and activity of alveolar macrophages that influence by metabolites produced by gut microbiota. The balance of gut microbiota composition plays an important role in maintaining the response of alveolar macrophages against infection.[6]

Microbiota studies in bronchiectasis patients found that *Haemophilus*, *Streptococcus*, and *Pseudomonas* were associated with the infection. Woo's study consisted of twenty-nine bronchiectasis patients who were followed for 16 years. The microbiota found were dominated by *Pseudomonas* and *Haemophilus*. The Bronchiectasis and Low-dose Erythromycin Study (BLESS) showed that *Haemophilus*-dominated patients had fewer exacerbations than *Pseudomonas*-dominated patients. Patients with *P.aeruginosa* infection had a worse outcome, more frequent exacerbations, decreased lung function, more sputum production, and a greater need for antibiotic therapy.[12–14]

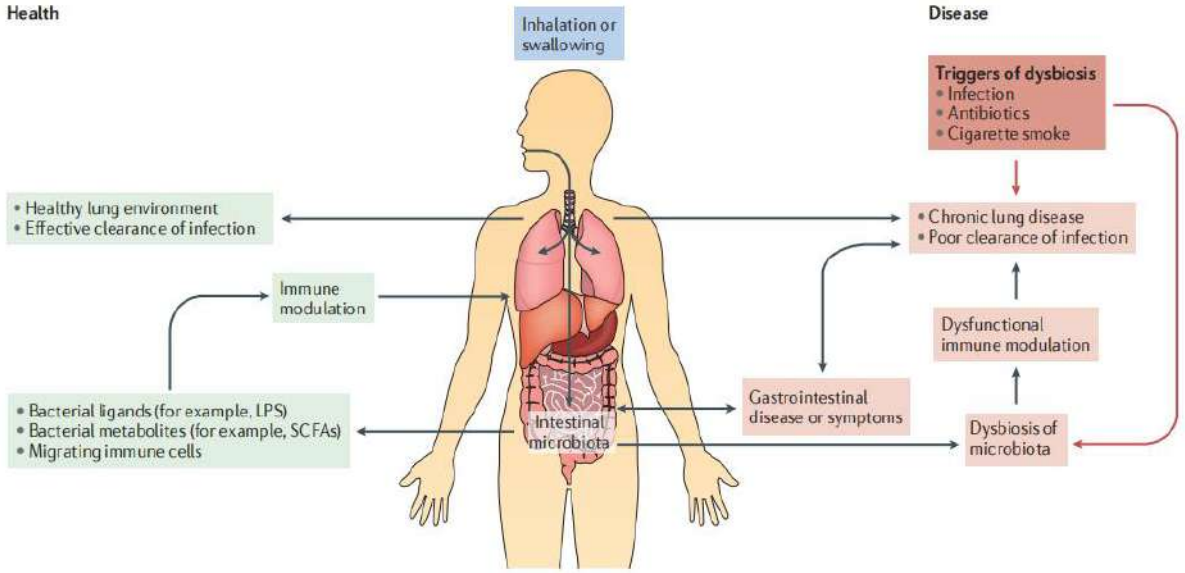


Figure 4. Interaction of immune system and intestinal microbiota in health and disease[5]

GUT-LUNG AXIS

The microbiota plays a vital role in tissue homeostasis. The complex interactions between the gut microbiota and the host immune system have crucial local effects on the gut and other tissues and organs such as the lung. Symptoms in the respiratory and gastrointestinal tract often coexist and lead to overlapping pathologies. This gives rise to a concept of the relationship between the intestines and the lungs called the gut-lung axis. Through this axis, changes in the composition of the gut microbiota not only cause abnormalities in the gut but also affect other organs in the respiratory system and cause disease.[1,2,11,15,16,3–10]

Research in rats has shown that the reduced bacterial microbiota in the gut caused by antibiotics can increase viral infections in the lungs. Another study in humans found differences in gut microbiota in COPD patients compared to healthy controls through fecal examination.[3,10]

Intestinal microbiota dysbiosis is associated with the pathogenesis and course of chronic lung diseases. Disturbances of the intestinal microbiota in early life can increase the risk of developing asthma. The intestinal microbiota also protects against respiratory infections. Decreased intestinal microbiota will interfere with the immune response as the viral or bacterial infection progresses in the respiratory tract, as shown in Figure 4. Intestinal microbiota plays a role in the formation and response of antibodies. Decreased intestinal microbiota due to antibiotic therapy can increase the number of bacteria in the blood and increase mortality.[1,3,4]

The concept of the gut-lung axis is a bidirectional interaction, a circle that can be stimulated from two sides.[1,10,17] The epithelial surfaces of the gastrointestinal tract and respiratory tract are exposed to various kinds of microbes. Ingested microbes can enter the gastrointestinal tract and then, through aspiration, can

enter the respiratory tract.[2,5,9] The intestinal and lung mucosa work as defenses against microbial penetration. Colonization between normal microbes and pathogenic microbes will stimulate an inflammatory response.[5] The transmission of commensal bacteria in the intestine, such as SFB, *Bifidobacterium*, and members of the genus *Bacteroides* also induces the formation of antimicrobial peptides, immunoglobulin A, and inflammatory cytokines.[5–7,15,16]

The lung microbiota is vital in the maturation and homeostasis of lung immunity. Colonization of the respiratory tract provides an important signal for local immune cell maturation. Pre-clinical studies have demonstrated a causal relationship between microbial colonization in the airways and regulation and maturation of immunity in the airways.[7]

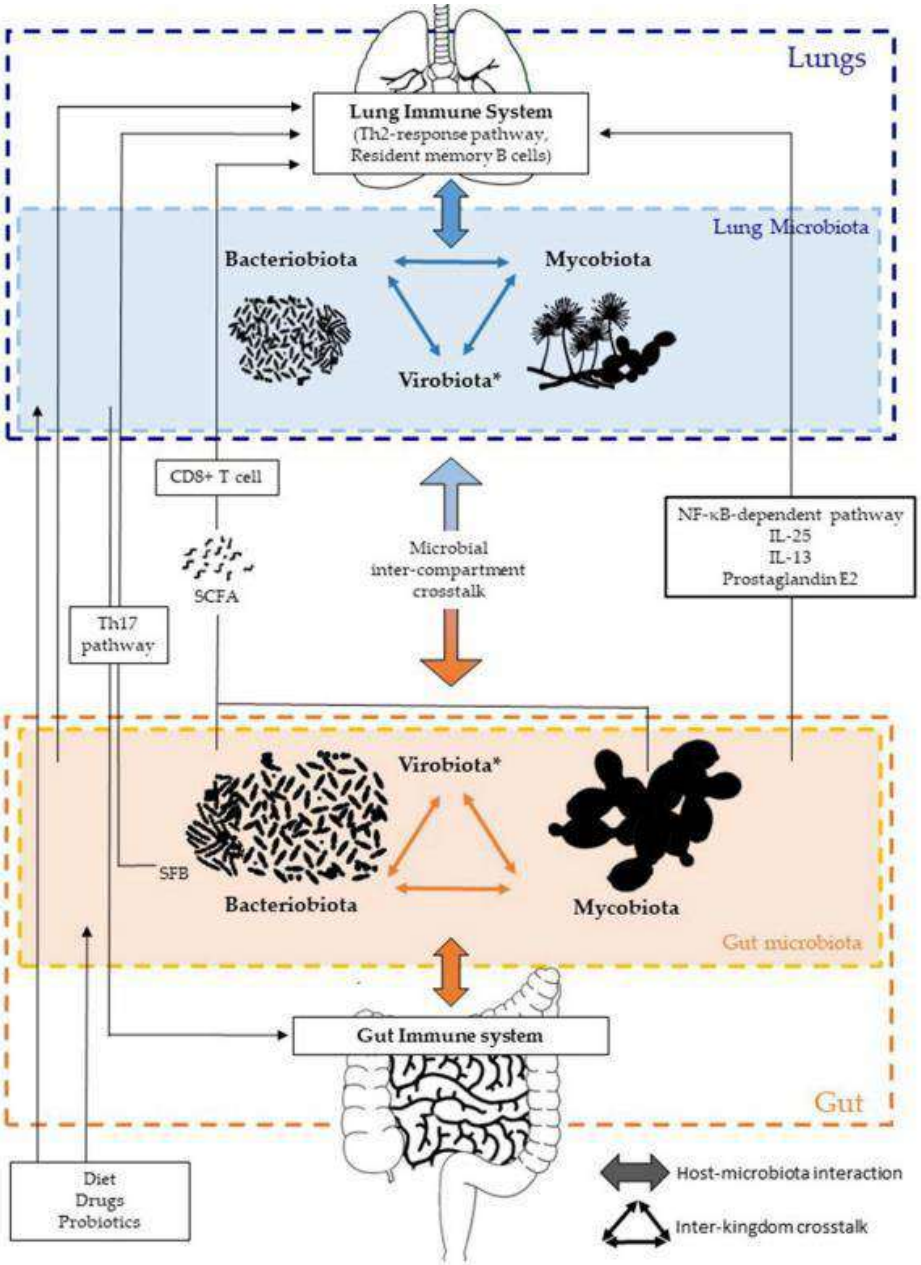


Figure 5. Inter-kingdom and inter-compartment in gut-lung axis[7]

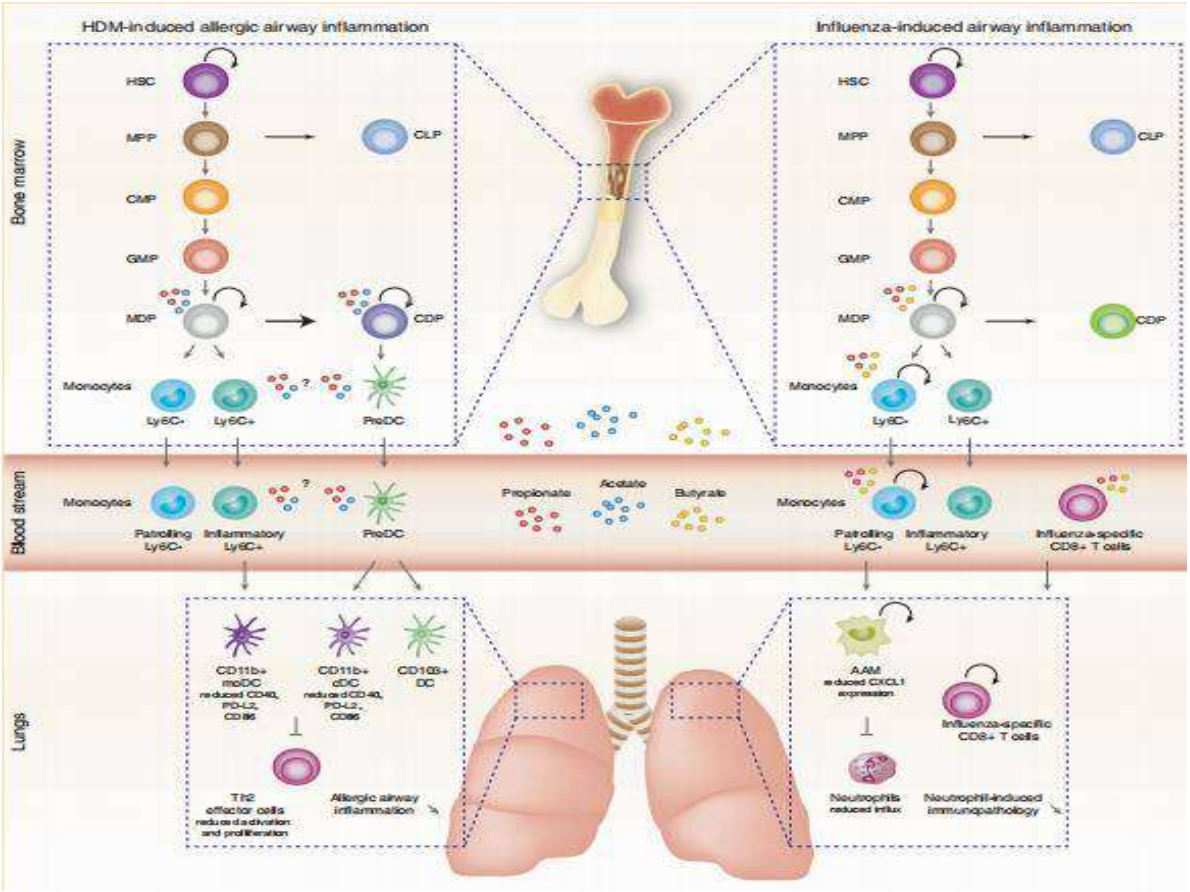


Figure 6. The effect of short chain fatty acid in bone marrow[2]

Figure 5 shows the relationship between components of the gut-lung axis system. Microbes interact with each organ via direct or indirect mechanisms. Intestinal microbes affect the immune system in the gut and lungs through local interactions or long-term interactions involving CD8+ T cells, Th17, IL-25, IL-13, prostaglandin E2, and NF-kB-dependent pathways. Lung microbiotas influence mucosal immunity and contribute to immune tolerance through neutrophil uptake, pro-inflammatory cytokines production mediated by receptor 2 (TLR2), and release of antimicrobial peptides such as Th17-stimulated β-defensin 2.[7]

Microbiota also produces metabolites. Fiber fermentation by gut microbiota produces short-chain fatty acids, with the most common types being propionate, acetate, and butyrate. These fatty acid products spread from the intestines to the bloodstream and can reach the bone marrow to stimulate the process of hematopoiesis. In the bone marrow, hematopoietic stem cells (HSCs) can differentiate into multipotent progenitors (MPPs), as shown in Figure 6. Furthermore, MPPs will differentiate into common lymphoid precursors (CLP), common myeloid precursors (CMP), granulocyte and macrophage precursors (GMP) and monocyte and DC progenitor (MDP).[2]

The MDP precursors will differentiate into monocytes such as Ly6C+, Ly6C-, and common dendritic cell precursor (CDP). When inflammation occurs, Ly6C+ cells will turn into CD11b high monocyte-derived

DCs (CD11b+ moDC), while CDP becomes pre-classical dendritic cells (pre-DC). Pre-DC cells will migrate from the bone marrow to the lungs and undergo maturation to become CD11b+ cDC. These maturation cells have a high phagocytic function but are less activated due to decreased expression of CD40, PD-L2, and CD 86. Thus, the ability of these lung DC to induce Th2 function and proliferation is decreased.[2]

Intestinal microbial diversity in early life may reduce inflammation in the airways mediated by the Th1 or Th2 balance. Another study used stool samples from pediatric patients diagnosed with asthma and healthy children as controls. In the asthma group, increased levels of inflammatory factors including CRP, TNF-α, IL-6, and decreased numbers of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* bacteria were discovered. These bacteria can suppress inflammation by increasing IL-10 and decreasing IL-12. This indicates that increased levels of inflammatory factors are associated with dysbiosis in the gut and increase the risk of asthma.[3,11]

Microbiota in the gut and lungs are important in fighting bacterial pneumonia. Lung microbiota plays a role in protecting tissues against infection by *Streptococcus pneumoniae* and *Klebsiella pneumoniae* by forming granulocyte-macrophage colony-stimulating factor (GM-CSF), which IL-17 stimulates. The gut microbiota also plays a role when a bacterial infection occurs in the lungs. Studies in mice have shown increased morbidity and mortality during acute lung infection by *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, or *Pseudomonas aeruginosa*. The use of broad-spectrum antibiotic therapy can disrupt the gut microbiota in mice and result in poorer outcomes.[2,6]

In COVID-19, gastrointestinal and respiratory tract disorders often coexist. Researchers then analyzed the gut microbiota of COVID-19 patients. The results found that in COVID-19 patients, the number of *Bifidobacterium*, *Lactobacillus*, and *Eubacterium* decreased. At the same time, pathogenic bacteria such as *Corynebacterium* (*Actinobacteria*) and *Ruthenibacterium* (*Firmicutes*) increased significantly. As the patient gets older, the diversity of the gut and lung microbiota decreases. Gut microbiota is impaired due to decreased function in elderly patients. These change in composition causes an imbalance in the microbiota and makes the immune system to weakened.[4,9]

The immune response induced by a viral infection in COVID-19 alters the gut microbiota leading to dysbiosis and increased intestinal permeability. This leads to secondary infections such as bacterial pneumonia. Under these conditions, increased intestinal permeability allows bacterial antigens and toxins to be translocated through the systemic circulation. This leads to sepsis and respiratory failure syndrome, due to dysfunction of the respiratory tract barrier. Another study by Vincent JL stated that endotoxin in patients with severe COVID-19 would increase. Gram-negative bacteria produce the toxin in the intestines.[18]

PROBIOTICS AND DIET ON THE GUT-LUNG AXIS

The gut microbiota can be affected by diet and lifestyle. Compared to an agrarian diet that consumes a diet low in fat and high in vegetables, a Caucasian diet high in fat and sugar content shows a significant decrease in *Bacteroidetes*. Children from Africa with a diet high in protein and fiber had higher levels of *Actinobacteria* and *Bacteroidetes*. Children from Western Europe with a high-fat and low-fiber diet showed higher levels of *Firmicutes* and *Proteobacteria*. SCFA content was four times higher in African populations with high concentrations of bacteria such as *Prevotella*, *Butyrivibrio*, and *Xylanibacter* to ferment polysaccharides from dietary fiber. The increase in SCFA causes a decrease in pH in the intestines, thereby reducing the number of pathogenic bacteria such as *Escherichia coli* and *Enterobacteriaceae*.[19]

Many studies have been conducted to evaluate the function of probiotics in the immune system. Research in mice indicates that T_{reg} cells that reduce allergic responses can be induced by administering probiotic bacteria such as *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, and *Bifidobacterium breve*. The administration of *Lactobacillus casei shirota* or *Lactobacillus rhamnosus* in cystic fibrosis patients showed a decrease in symptoms of exacerbations. Probiotics also improve inflammatory conditions in Irritable Bowel Disease (IBD) patients by regulating innate immunity through TLR. Probiotics increase the defense function in the intestine by producing bactericidal substances that will fight pathogenic bacteria.[1,19]

CONCLUSION

Microbiota plays a role in the formation and maturation of the immune system. In contrast, the immune system shapes the composition and function of the microbiota that influence the inflammatory response in the body. The gut-lung axis is the interaction between the gut and the lungs. Changes in the composition of the gut microbiota not only cause abnormalities in the intestine but also affect other organs such as the lungs and cause diseases in the respiratory tract. Through these interactions, an approach through the gut microbiota could be useful in the management of pulmonary diseases.

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Literature Review

Management of Febrile Neutropenia in Lung Cancer

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Abstract

Febrile neutropenia (FN) is defined as an oral temperature of >38.3° C or two consecutive measures >38°C within 2 hours accompanied by an absolute neutrophil count (ANC) of 500/L or a predicted decrease below 500/L in individuals undergoing systemic chemotherapy for cancer. FN is one of the oncological emergencies that can influence cancer patients' outcomes since it can increase morbidity, treatment delays, decrease survival, and expand costs. The incidence of FN is 3.7-28% in lung cancer patients. Mortality associated with FN episodes is 15%. FN risk factors include chemotherapy regimen, age, comorbidities, mucositis, performance status, and previous FN history. Validated predicted instruments such as The Multinational Association for Supportive Care in Cancer (MASCC) or The Clinical Index of Stable Febrile Neutropenia (CISNE) score could assist in the risk assessment of FN and determine advanced management. Effective therapy of FN requires investigation of diagnosis as soon as possible and acknowledging the potential source of infection. The prophylactic granulocyte colony-stimulating factors (G-CSF) and anti-microbial successfully reduced mortality due to FN.

Keywords: antibiotics, febrile neutropenia, G-CSF, lung cancer

INTRODUCTION

Globally, lung cancer is the leading cause of cancer-related mortality. Global cancer statistics (Globocan) predicted 2.2 million new cases of lung cancer (11.4% of all cancer cases) and 1.79 million cancer-related fatalities (18.0% of all cancer-related deaths) in 2020, both of which were higher than in 2018 (1,76 million deaths and 2,09 million new cases).[1]

According to Globocan 2020 data, lung cancer fatalities in Indonesia rose to 30,843 (13.2% of all cancer deaths), with new cases reaching 34,783 (8.8% of total cancer cases). It made lung cancer the most frequent cancer and the main cause of cancer deaths in both genders.[2] Non-small cell lung cancer is the most common histologic form of lung cancer (85% of all cases) (NSCLC).[3]

The standard chemotherapy management for NSCLC is platinum-based. The suggested neoadjuvant chemotherapy in stage II (A/B) and stage IIIA NSCLC is doublet platinum chemotherapy. In advanced NSCLC, chemotherapy combination radiotherapy or chemotherapy

alone; however, the current first-line standard management is based on the outcomes of molecular testing. For instance, in stage IV NSCLC for tumors with EGFR mutation-positive, first-line therapy is EGFR tyrosine kinase inhibitors, and anaplastic lymphoma kinase (ALK) inhibitors are the first-line management suggested for ALK-rearranged NSCLC patients.[4,5]

The 5-year survival rate for NSCLC patients is dismal, ranging between 10 and 20%. Platinum-induced myelosuppression is a side effect of chemotherapeutic induction in NSCLC.[4] Certain chemotherapy drugs (e.g., carboplatin/docetaxel, cisplatin/etoposide) have been linked to an increased incidence of chemotherapy-induced neutropenia (CIN) or febrile neutropenia (FN).[6] The previous research reported that 10-20% of NSCLC patients treated with docetaxel and ramucirumab develop FN.[7]

According to additional studies, FN occurs in approximately 26% of docetaxel-based chemotherapy cases. FN is the most common cause of treatment-related morbidity in small cell lung cancer (SCLC) patients, with previous research analyzing a 6.8-9.5% prevalence of FN-related morbidity in hospitalized patients.[8]

There is a direct correlation between the degree of neutropenia and the dosage of chemotherapy. The chemotherapy regimen, age, comorbidities, history of FN, absence of prophylactic anti-microbials or granulocyte colony-stimulating factors (G-CSF), the status of performance, mucositis, and cardiovascular disorder are several individual risk factors that have been identified in FN.[8]

FN is a medical oncology emergency since it can raise morbidity, delay therapy, decrease survival rate, and increase expense, all of which can impact treatment success.[9] To avoid FN as soon as possible, there must be sufficient concern. This literature review will elaborate on FN as a major lung cancer consequence.

FEBRILE NEUTROPENIA IN LUNG CANCER

Definition

In cancer patients, the incidental fever with CIN is life-threatening and may need empiric broad-spectrum antimicrobial treatment. Even though the infection contamination is suspected to be the source of fever, it is troublesome to decide the pathogenic cause in most cases. Klastersky named this condition in 1990 FN, defined by:[6,10]

1. Oral temperature >38.3°C or >38°C within 2 hours in two sequent measurements.
2. Neutrophil count/ absolute neutrophil count (ANC) <500/µl or <1,000/µl with a presumed to reduce to <500/µl within 48 hours.

The ANC is measured by multiplying the WBC (white blood cell) count by the percentage of segments and bands.

Incidence

The incidence of FN reached 31% in lung cancer patients, according to Moreira-Pinto et al.[11] The prevalence may vary

based on the antineoplastic regimen used. The incidence of FN may decrease due to the therapeutic impact of G-CSF therapy.[12]

The retrospective study revealed an incidence of 58.3% for neutropenia and 8.3% for FN in advanced NSCLC patients undergoing platinum-based chemotherapy doublets.[13] Fujiwara et al research showed the incidence of FN was 20% in lung cancer patients in Japan who had never received chemotherapy while receiving etoposide and platinum in combination.[8]

Another study revealed that the incidence of FN in lung cancer patients after doublet platinum treatment ranged from 3 to 14%.[14] According to past studies, mortality risk is at least 15% lower for individuals without FN than for patients with FN.[15] Previous studies have identified that FN is responsible for a 6.8–9.5% of death among in-hospital patients.[8]

Risk Factors

Although faulty, the scoring methodology can aid in recommending clinical scoring indicators for advanced care (e.g., hospital versus outpatient, parenteral versus oral) and initial empiric antimicrobial treatment.[10,16] Validated scoring systems used to predict the defy of medical complexity in FN consist of:

1. Talcott Score. Talcott et al created a clinical prediction score that categorized patients into four risk categories. For instance, only 5% of outpatients with FN, well-managed cancer, and minor comorbidities are likely to experience severe consequences. This classification is prospectively verified in research undertaken at two chemotherapy-accepting centers in the United States.[10]
2. Multinational Association for Supportive Care in Cancer (MASCC). Table 1 demonstrates that a score of 21 points or more hints at a low risk of complications.[10]

Table 1. MASCC index risk[10]

Characteristics	Score
A burden of illness*; absence or mild symptoms	5
A burden of illness; absence or moderate symptoms	3
A burden of illness; absence or severe symptoms	0
No low blood pressure (systolic BP > 90 mmHg)	5
Absence of chronic obstructive pulmonary disease (COPD)	4
Solid tumor/lymphoma with no history of infection of fungal	4
The dehydration is none	3
Outpatient status (at the onset of fever)	3
Age <60 years	2

Note: *Burden of illness is a subjective characteristic based on symptom severity determined by the attending physician at presentation.

3. The Clinical Index of Stable Febrile Neutropenia (CISNE). The CISNE divides patients into three risk categories: low (0 points), intermediate (1 to 2 points), and high (>3 points) (shown in Table 2).[10]

Table 2. CISNE score[10]

Characteristics	Score
Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2	2
Stress-induced hyperglycemia	2
COPD	1
Chronic Cardiovascular Disease	1
Mucositis National Cancer Institute (NCI), grade ≥2	1
Monocyte <200 per µL	1

A retrospective analysis study by Fujiwara et al determines a male gender and the previous radiotherapy as independent risk components for FN in patients treated with Cisplatin-Etoposide.[8] The characteristics of patients with a low and high risk for serious complications in FN are presented in Table 3, respectively.

Pathogenesis

Factors contributing to the pathophysiology of FN include chemotherapy's direct effects on the mucosal barrier and immune system and buffers in host defense linked to underlying malignancy.[9,17]

Chemotherapy will disrupt blood cell formation, causing neutropenia; other than that, chemotherapy also causes injury to the gastrointestinal (GI) mucosa, which induces mucosal barrier damage that actuates infection contamination. Using catheter indwelling will also increase access to tissues that can initiate bacterial colonization (Figure 1).[9,18] Most scenes of FN are related to microorganisms from the endogenous gastrointestinal flora that invade the circulatory system,[17] and cancer-associated immunosuppression is considered to be an essential pathogenesis factor of FN.[9]

Diagnostic Investigation

The initial assessment and investigation of FN are also essential to require a history of chemotherapy, previous prophylactic antibiotics, steroids, recent surgical procedures, and a history of allergy.[19,20]

Table 3. Characteristics of low and high risk for severe complications in FN[9]

Risk	Characteristics
Patients with any of the following are willfully at **low risk** for thought-full complications amid an FN scene	a. Outpatient when fever occurs b. Not associated with acute comorbid disease c. Anticipate a short period of severe neutropenia (≤100 cells/ml for <7 days) d. Performance Status is good (ECOG 0-1) e. Absence of hepatic or kidney disorder f. MASCC risk index score ≥ 21 or CISNE <3
Patients with any of the consecutive characteristics are contemplated to be at **high risk** for deliberate complications during an FN scene	a. Patients accepting adequate myelosuppressive cytotoxic treatment to cause extreme neutropenia (ANC <500 cells/ml) for >7 days b. MASCC risk index score <21 c. CISNE score ≥3 (in patients with solid tumors) d. Presence of uncontrolled active comorbidities: 1) Indicators of sepsis or septic shock (e.g., hemodynamic instability, new-onset mental status changes, respiratory dysfunction, oliguria) 2) Mucositis of the mouth or gastrointestinal system causes severe diarrhea or impairs swallowing. 3) Gastrointestinal manifestations, along with nausea and vomiting, abdominal pain, or diarrhea 4) Intravascular catheter infections, especially tunnel catheter infections 5) Current lung infiltrates or hypoxemia 6) History of chronic lung disease 7) Current complex infection e. Use of Alemtuzumab or CAR-T cells in the last two months f. Uncontrolled or progressive cancer g. Mucositis Grade 3-4 There is data of hepatic impairment that aminotransferase level > five times normal value or renal impairment that creatinine clearance <30 mL/min

Initial assessment and investigation of FN include:[19,20]

a. Attendance of indwelling IV catheters.
b. Respiratory system, gastrointestinal system, skin, perineal/ urogenital area, oropharynx, central nervous system symptoms or signs.
c. Awareness of previous positive microbiological outcomes by reviewing clinical data.
d. Routine inspections:
    1) Complete blood count, coagulation factors, C-reactive protein (CRP);
    2) Blood cultures (minimum two times), including cultures from indwelling IV catheters;
    3) Urinalysis and culture*, Sputum microscopy and culture*, Stool microscopy and culture* (Note: *Urinalysis, sputum, and stool cultures are onliest if a focus of infection in the area is suspected);
    4) Skin lesions (aspiration/biopsy/ swab);
    5) Chest X-ray.
e. Other examinations (profound/ prolonger neutropenia/ following allografts), High-resolution chest CT (if fever >72 hours with antibiotics), bronchoalveolar lavage.

Treatment

Several chemotherapeutic drugs pose a greater risk for CIN or FN. It may result in dose reduction and chemotherapy delay, reducing treatment success.[8,9] Therefore, CIN/FN prophylaxis must guarantee that cytotoxic treatment is administered on schedule and at the correct dose.[6,9] Antimicrobials and G-CSF have been used effectively to prevent chemotherapy-associated FN. Matsui et al observed that prophylactic long-acting G-CSF lowered the occurrence of FN in advanced NSCLC patients receiving docetaxel monotherapy.[21]

Effective management of FN requires immediate diagnosis and acknowledgment of potential infections. Daily symptom monitoring is urgent to teach in outpatients. Recognize FN earlier and creating a time-dependent calculation for establishing the diagnosis quickly and medicating cancer patients with FN and suspected sepsis is vital (Figure 2).[6,9,22]

Antibiotic Therapy

Antibiotics ought to be given as soon as conceivable. Prior studies recommend that patients with FN start empiric broad-spectrum antimicrobial treatment as soon as a blood culture is obtained. Empirical antibiotics can be considered based on the pathogenic organisms frequently found in FN. Gram-negative, such as *E. coli*, *P. aeruginosa,* or gram-positive such as *S. pneumonia* or *S. aureus*.[6,9,11]

According to the international guideline, FN patients suggest empirical antibiotics treatment within 60 minutes of onset (Figure 2). They are starting empiric antibacterial treatment as soon as possible to avoid developing sepsis and death. Early regimen selection should consider the patient history, allergy history, clinical symptoms and signs, recent use of antimicrobial agents, culture information, and local hospital bacterial patterns.[6,9,11,22]

Considering the risk of a resistant organism is the underlying factor of empirical therapy options and targeted therapies after the pathogenic bacteria have been identified.[6,9,11,22]

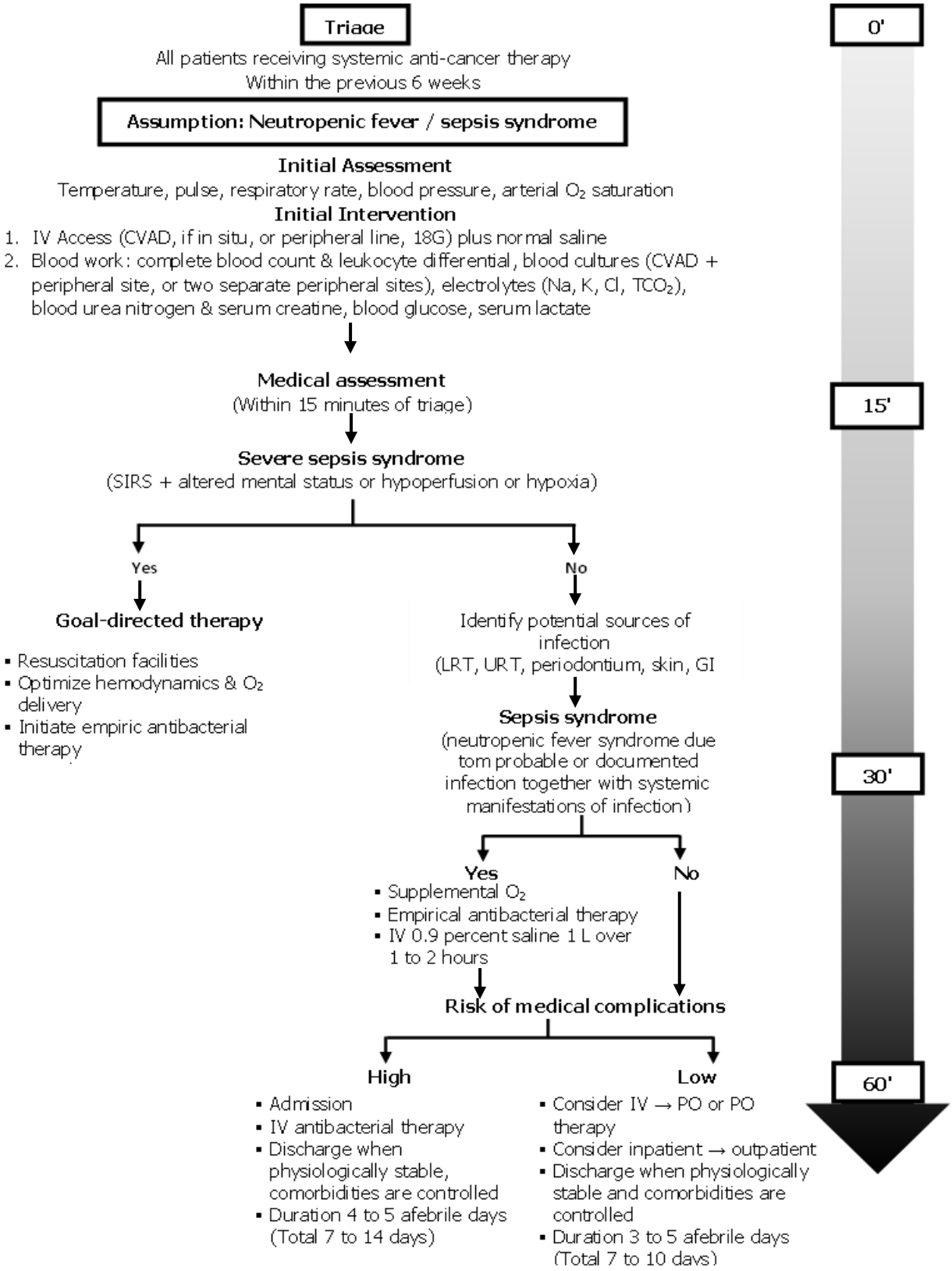

Figure 2. Initial assessment and management of cancer patients with FN and suspected sepsis based on a time-dependent algorithm[22]

Prior to obtaining bacterial culture results, empirical antibiotic treatment is based on the consideration of the most virulent and common pathogens that might cause significant disease or death. Based on the risk of infection and the clinical presentation, using a beta-lactam having antibacterial action against *P. aeruginosa* is recommended in monotherapy or in combination with another regimen.[6,23]

To inhibit the expansion of bacterial infections as a complication of neutropenia, prophylactic with antimicrobials is necessary. However, its usefulness in CIN is still controversial. According to Escrihuela et al, individuals at high risk for FN problems should consider hospitalization and beginning empirical antibiotic therapy (CISNE score 3).[23]

Antimicrobial treatment in neutropenic patients lowered the number of deaths, fever episodes, and bacterial infections. According to Lucas et al meta-analysis of 52 trials, including patients with neutropenia and predominantly hematologic malignancies, Quinolones are helpful in preventing bacterial infections without inducing resistance.[9]

The percentage of positive microbiological findings with conventional blood cultures is determined using antimicrobials as preventatives. Overall, in ±19% of FN patients, bacteremia can be identified.[11] Antibiotic-resistant bacteria, such as extended-spectrum-lactamase (ESBL), methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE), are becoming more prevalent. Infections with Candida strains resistant to fluconazole (such as Candida krusei and Candida glabrata) are also rising. Antifungal prophylaxis with oral triazoles or parenteral echinocandins is recommended for individuals at risk for severe and extended neutropenia. For solid tumors patients, prevention with antifungals is not routinely given.[6,9]

MASCC or CISNE score as a validated instrument could be used to evaluate the possibility of complications in FN patients, and the recommendation is as follows:[9,10]

1. The risk of complications was low in FN patients (Table 3). Oral antibiotics could be given in this category, and if a good follow-up could be done, it could be outpatient. Parenteral regimens also could be given in some low-risk outpatients. Antibiotic choices are Ciprofloxacin + Amoxicillin/Clavulanate or Moxifloxacin, or Levofloxacin. The combination of quinolones with amoxicillin-clavulanic acid is not superior to single-agent quinolones. However, the increase in gram-positive infections in FN makes the former strategy preferable. Several reviews have supported the safety of switching to oral medication from intravenous therapy early in patients who have not had a fever for at least 48 hours.[6,9,24]
2. The risk of complications was high in FN patients (Table 3). Patients in this category must be hospitalized and not be delayed in administering broad-spectrum antimicrobial therapy. Patients must be observed to evaluate hemodynamic stability (pre-shock).

Antipseudomonal beta-lactams, such as cefepime, imipenem/cilastatin, meropenem, carbapenem, and piperacillin-tazobactam, are the intravenous antimicrobials of choice for hospitalized patients at high risk. However, antimicrobial medicines utilized in patients with solid tumors are scarcely documented. A meta-analysis assessing the efficacy of single-agent versus combination therapy revealed equal efficacy. Meropenem is one of the most commonly utilized antimicrobial medications in FN., while carbapenem is an alternate antibacterial treatment.[6,9] Numerous studies have indicated that carbapenem is one of the initial treatments for FN in both adults and children and is more effective in reducing all-cause mortality than anti-pseudomonas penicillin and fourth-generation cephalosporins.[25] However, Tang et al, found no difference between carbapenems and beta-lactam monotherapy or combination therapy in their investigation.[26] Intravenous combination anti-microbials are considered in case antimicrobial resistance is suspected.[9]

Granulocyte colony-stimulating factors (G-CSF)

The granulocyte colony-stimulating factor (G-CSF) administration as prophylaxis is recommended by The American Society of Clinical Oncology (ASCO) guidelines when the risk of FN is ≥20%.[8] G-CSF stimulates white blood cells (WBC), a biological growth factor promoting the proliferation, differentiation, and activation of neutrophils in the bone marrow. The efficacy of standard G-CSF agents (Filgastrim) and pegylated agents (Pegfilgastrim) as FN prophylaxis has proven to lower the risk, severity, length of FN episodes, and the troubling effects of chemotherapy.[6,9]

Several meta-analyses show that G-CSF as primary prophylaxis can lower the risk of FN by a minimum of 50% in solid tumors.[7] The administration of G-CSF and a granulocyte-macrophage colony-stimulating figure (GM-CSF) as primary prophylaxis in patients with a 20% or more risk of developing CIN/ FN is suggested by most international guidelines.[6,9]

As an example, those receiving high-risk chemotherapy regimens and risk factors that may intensify all patient-associated chance of CIN/FN, such as age >65 years, comorbid, history of chemotherapy, cancer type, chemotherapy regiment, the intensity of planned dose, the onset of leukopenia, hepatic and kidney disorder). Studies showed that patients with established FN who received MGFs in addition to antibiotics had a shorter time on IV antibiotics and a shorter hospital stay but no change in overall survival.[6,9]

At 24-72 hours after the last day of chemotherapy, filgrastim is delivered subcutaneously (sc) at a dosage of 5 g/kg/day until steady post-nadir ANC recovery. Pegfilgrastim 100 g/kg (individual) and a total dose of 6 mg (a common practice) are equally effective. There are no acceptable data for reducing the standard number of days and dose of

G-CSF, and The European Medicine Agency (EMA)/United States Food and Drug Administration (FDA) has approved using biosimilars.[27]

Therapeutic Response

The assessment of therapy response from clinical symptoms and ANC, as below:[28]

a. Oral antibiotics should be recommended if the patient has no fever and an ANC $\geq 0.5\times10^9$/l within 48 hours, with minimal risk and no focus infection.
b. The patient is at high risk without the cause of infection and receives a combination antimicrobial treatment. The aminoglycoside can be discontinued.
c. When the cause of infection is found, antibiotic administration is continued according to a specific therapy.
d. The patient is still febrile but clinically stable after 48 hours; continue early antibiotic therapy.
e. If the patient is clinically unstable, replace or expand antimicrobial treatment according to clinical considerations. Some centers add glycopeptide or replace the agents with imipenem, meropenem, and glycopeptides. Uncommon infections should be considered, especially in cases of elevated CRP. Imaging studies of the thorax and upper abdomen should rule out fungal infection or abscess. When fever persists for more than 4-6 days, empiric antifungal treatment may be required.
f. Asymptomatic patient with the ANC is $\geq 0.5\times10^9$/l, has no fever for 48 hours, and the blood culture is negative. Discontinue antibiotics.
g. Patients do not experience complications with the ANC is $\leq 0.5\times10^9$/l and no fever for 5-7 days; discontinue antibiotics, except in certain high-risk cases. After high-dose chemotherapy, antibiotics are usually extended for ten days or until the ANC is 0.5×10^9.
h. Even though neutrophil has improved, the patient with persistent fever should be assessed by a clinical microbiologist, and antifungal therapies are considered.

Prognosis

Mortality associated with the FN episode was 15%, with 53.8% being culture positive, creating a poor prognosis of FN. The existence of focus infection (e.g., pneumonia, abscess, cellulitis) also worsens outcomes. Moreira-Pinto et al found that one predictive factor of increased mortality in FN patients was ANC $<100/\mu L$.[11]

The investigation by Kauffmann-Guerrero et al, in 39 SCLC patients in Germany, reported that patients with FN showed significantly shorter PFS than those without FN. Chemotherapy interruption, delay, or dose reduction made these conditions, and therefore, the degree of remission in the patient was reduced. In the FN versus non-FN group, patients with at least one postponed chemotherapy administration are 75% and 35%,

respectively. In FN patients, the immune response to tumor cells may be impaired; those with an inadequate immune response may be more susceptible to FN and slightly to form an antitumor immune response.[29]

CONCLUSION

Febrile neutropenia (FN) continues to be a major problem for chemotherapy-treated lung cancer patients, leading to poor quality of life and even death. Risk variables are identified, including patient characteristics (age, performance status), underlying disorders (staging, comorbidities), and chemotherapy regimen. Assessing the risk of FN complications using proven prediction instruments, such as the MASCC score, is recommended. The management of FN with antimicrobials and G-CSF has been successful in lowering FN-related mortality.

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Literature Review

Upper Airway Resistance Syndrome: An Underdiagnosed Sleep-related Breathing Disorder

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Abstract

Upper Airway Resistance Syndrome (UARS) is an example of a sleep-related breathing disorder. UARS was first reported by Guilleminault in 1992 and it is known as excessive daytime sleepiness without obvious apnea or hypopnea that is characterized by more than 50% of respiratory effort-related arousals (RERAs) during sleep. The prevalence of UARS was 15% in the population of São Paulo. Although clinical manifestations, electroencephalogram (EEG) findings, and pathogenesis differ between UARS and OSA (Obstructive Sleep Apnea), it still sparked a debate among researchers as to whether UARS should be categorized as a distinct disorder. The International Classification of Sleep Disorders - Third Edition (ICSD3) integrated UARS into OSA diagnosis, resulting in underdiagnosed and undertreated patients with sleep-related breathing disorders who did not necessarily meet OSA criteria. Untreated UARS, on the other hand, has a variety of clinical consequences, including poor weight and height growth, daytime irritability, worsening of quality of life, and cardiovascular complications. Continuous positive airway pressure therapy, oral appliances, surgical management, weight reduction, and positional therapy are all considered options in the management of UARS.

Keywords: sleep-related breathing disorder, upper airway resistance syndrome

INTRODUCTION

Sleep-related breathing disorders, also known as SRBD, are common sleep disorders that may lead to serious complications. SRDB refers to a group of diseases that include central sleep apnea (CSA), obstructive sleep apnea (OSA), upper airway resistance syndrome (UARS), isolated primary snoring (PS), and obesity hypoventilation syndrome (OHS).[1] Mild Obstructive Sleep Apnea (OSA) and Upper Airway Resistance Syndrome (UARS) are both included in Mild SRBD.[2]

One definition of UARS is the existence of excessive daytime sleepiness without apparent explanation that is linked to more than 50% of non-apneic and non-hypoxic respiratory events in sleep (i.e., RERAs). A gradual increase in respiratory effort is a hallmark of RERAs.[3]

Guilleminault first identified UARS in 1992 through his publication of a case series presenting patients who displayed greater respiratory muscle effort when they

slept as a result of excessive upper airway resistance and elevated negative endo-oesophageal pressure. The respiratory efforts are linked to arousal and sleep disruption/fragmentation. A new diagnosis of UARS was designated because these patients did not fulfill OSA criteria. Furthermore, the theory stated that patients with UARS had enhanced sensitivity to respiratory effort due to airway resistance, resulting in recurrent arousals known as RERAs (compared with arousals in patients with OSA who generally happened as a response to obstruction of higher degrees such as hypopnea and apnea).[4]

The classification of UARS as a novel condition of sleep-disordered breathing sparked debate. The authors of the International Classification of Sleep Disorders - Third Edition (ICSD3) included RERAs into OSA diagnostic criteria to reduce the necessity for UARS to be classified as a separate condition; nonetheless, the relevance of UARS does not stop with its incorporation into OSA. There are still patients who fulfill the diagnosis of UARS but are not included in the definition of OSA by ICSD3 and are not diagnosed as having sleep-disordered breathing disorders. It is important to consider that sleep-disordered breathing may exist outside the scope of ICSD3. As a result, UARS remains a syndrome under investigation by researchers.[4]

UARS often continues to be stable over time. In some cases, if the patient's body mass index (BMI) rises, UARS could develop into OSA.[5] Finding a method to objectively identify sleep has been one of the fundamental issues in sleep medicine. More than ten years after the original description, people with UARS are still frequently undiagnosed and untreated.[6]

The lack of respiratory events detected in PSG frequently delays the diagnosis of UARS. These people visited the sleep clinic with complaints of daytime sleepiness or exhaustion.[7]

They underwent a PSG afterward, which revealed no OSA. These patients' symptoms, which include exhaustion, loss of energy, agitation, and a decline in memory and attention, may have been confused with other medical conditions, such as chronic fatigue syndrome, idiopathic hypersomnia, lack of sleep, asymptomatic habitual/persistent snoring, and other disorders related to psychiatric. These individuals were not recommended for treatment and were misdiagnosed as not having sleep-related breathing disorders.[7]

UARS has many clinical consequences, including poor weight and height growth (resulting from reduced growth hormone secretion during sleep), decreased academic performance, and daytime irritability.[8]

According to several pieces of research, UARS patients are more likely to be involved in road accidents. UARS is related to a greater likelihood of accidents among drowsy drivers.[7] Therefore, every sleep physician must be aware of UARS so that patients can receive early and proper treatment.[9]

EPIDEMIOLOGY

The prevalence of UARS worldwide is not yet fully established due to different criteria employed in the studies. Cases presenting pure UARS are considered rare in clinical settings.[10,11] In a retrospective analysis of all polysomnographic conducted at a military academic sleep disorder center throughout the year 2000, it was found that UARS prevalence was 8.4%. Four of the UARS cases had neither reported snoring through history taking nor found any evidence of it during polysomnography.[10,12]

In a more recent investigation with a sample that is taken from the São Paulo population, the prevalence of UARS was 15%. The sample is taken by utilizing the existence of limitation in inspiratory flow linked to symptoms to identifying UARS.[13]

According to Guilleminault and Chowdhuri, patients with UARS are more likely to be younger and more often happened in females compared to OSA/Hypopnea patients.[14] In comparison to OSA patients, UARS patients were noticeably less likely to be overweight or obese and had less weight gain over the previous five years. In contrast with what is frequently seen in patients diagnosed with OSA, UARS patients are more frequently non-obese, presenting body mass index (BMI) under 25 kg/m^2.[9]

UARS group also appears to have the largest female-to-male ratio.[10,11] Patients with UARS also more frequently report fatigue and sleep-onset insomnia. Furthermore, in comparison to patients diagnosed with OSA/Hypopnea, patients with UARS had a higher prevalence of orthostatic intolerance, according to Guilleminault and colleagues.[14]

Comparative studies have focused on the differences between the complaints and symptoms of UARS and OSA to distinguish more clearly between the two syndromes, with Upper Airway Resistance Syndrome more frequently occurring in pre-menopausal women and being characterized by less snoring along with reports of unrefreshing sleep, additional complaints of "fatigue during daytime", poor concentration, memory problems, difficulty performing at work, mood syndromes, and unspecific muscle pain.[6]

PATHOGENESIS

In some ways, the pathophysiology of UARS is thought to resemble the pathophysiology of OSA. However, other researchers have claimed that some elements are suggesting UARS is a different entity with a distinct pathogenesis compared to OSA. Different upper airway responses are dissimilarities. There are differences between UARS and OSA in terms of the absence or presence of neurogenic lesions caused by persistent trauma associated with irregular breathing. A study conducted by Friberg pointed out that in the upper airway of patients with OSA, there are local neurogenic lesions that are related to the slow conduction of impulses.[9]

According to research by Afifi et al, OSA exhibits an aberrant response to

potentials evoked related to respiration, which suggests a particular diminishing of cortical processing of information related to inspiratory effort.[9]

It may be concluded that neurogenic lesions present in OSA patients' upper larynx and pharynx may disturb the normal control of patency of the upper airway, resulting in episodes of apneas, as well as hypopneas, due to an imbalance between the effort of intrathoracic and contractions of upper airway muscle driven on by impairment of local sensory nerves. Research showed that there is a local polyneuropathy that involves very small sensory fibers and motor fibers that innervate the upper airway in OSA patients. Some researchers concluded that patients with Upper Airway Resistance Syndrome rarely display these localized destructions.[9]

Studies suggested that the pathophysiology of UARS and OSA may differ. When the upper airway's sensory input is blunted or eliminated in OSA, the muscular tone is more likely to have problems, which causes the upper airway to narrow at the start of inspiration and eventually collapse. Although patients with UARS have a small airway due to structural changes at the point with varying locations, starting from the nose's external valve to the tongue's base, the non-existent neurogenic lesions in upper airways, accompanied by persistent sensory input may cause faster arousal.[9]

Patients with OSA and UARS have been shown to have different effects and changes in the autonomic nervous system (ANS). The decline of oxygen saturation and arousal may cause the sympathetic tone to become hyperactive in OSA. Inhibition of sympathetic tone is found in UARS participants due to abnormal inspiratory effort which is related to higher airway resistance. Mild orthostatic and vagal dominance during sleep is a result of the release of the vagal tone.[9]

To summarize, reflexes of the upper airway remain intact in UARS patients both during sleep and wake, unlike reflexes in OSA patients. Moreover, in OSA patients, recurrent decreases of SaO2 may excite the sympathetic tone throughout sleep, resulting in escalating reset and hyperactivity of sympathetic tone, a response that is absent in UARS.[3]

In conclusion, UARS was more dominated by respiratory effort-related arousals (RERAs) while apneas and hypopneas become the main respiratory events in OSA. Upper airway collapsibility is more often severe in OSA while in UARS it is considered intermediate.[3,9]

CLINICAL MANIFESTATIONS

Unexplained arousals in UARS patients are connected with increased effort of respiration, this may lead to fragmentation of sleep, which manifests as disruptions during sleep and awakening that is unexplained. This condition frequently occurs 2-3 hours after sleeping. Sleep fragmentation may result in fatigue and excessive daytime sleepiness, these symptoms are the most common findings in UARS.[15]

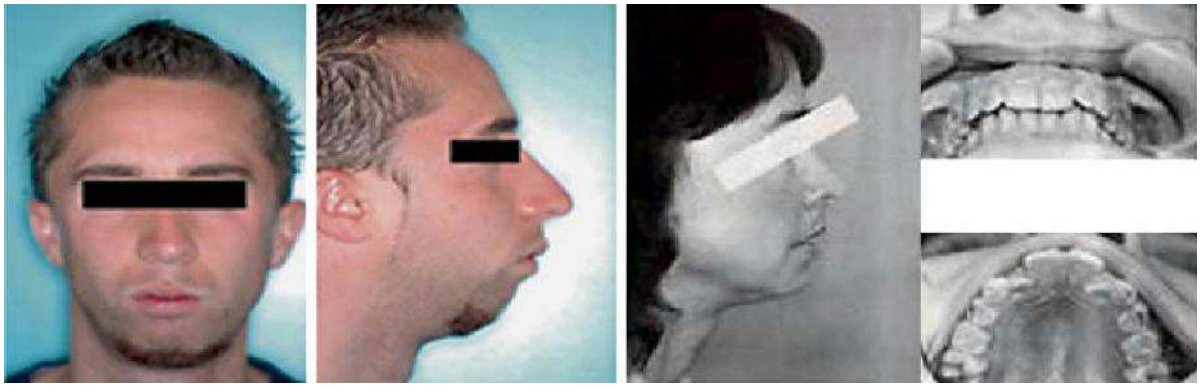

Figure 1. Typical craniofacial features in UARS patients[10]

In addition, UARS patients also have a much higher rate of postural hypotension, insomnia which occurs on the onset of sleep and sleep-maintenance insomnia, gastric reflux, headaches, vasomotor rhinitis, anxiety, irritable bowel syndrome, and alpha-delta sleep.[14,16] Chronic insomnia is also more commonly found in UARS patients. Parasomnias symptoms including sleep terrors and sleepwalking and are also presented in UARS.[9] Other manifestations of UARS include myalgia, difficulty in concentrating, and bruxism.[3]

UARS can develop even when snoring is absent. Sleep-disordered breathing without clinically obvious snoring has already been described in the literature. Guilleminault and colleagues found that more than one-fourth of patients with UARS did not report snoring in a study of sleep-disordered breathing in postmenopausal women.[12]

Individuals with untreated UARS might show a quality of life that is poorer compared to normal individuals. They may also suffer from cardiovascular complications. Exhaustion, sleeplessness, and depressive mood are common sleep and daytime symptoms in untreated UARS, and they frequently get worse over time. Characteristic negative esophageal pressure (Pes) in UARS might result in a diastolic leftward shift of the interventricular cardiac septum and, as a result, may progress into ventricular "collapse." Long-term flow limitation events may create a minor rise in end-tidal carbon dioxide (PetCO2), which can trigger sympathetic nervous system activity. This might result in hypertension, as well as cardiovascular and metabolic effects. In non-treated UARS patients, a rise in inflammatory markers is possible.[16]

Physical examination of UARS patients may reveal a variety of abnormalities, including narrowing of external nasal valves, the collapse of the internal nasal valve, nasal turbinate hypertrophy, and deviation of the septum. UARS-related craniofacial alterations are also discussed. Patients with UARS have been reported to experience cold extremities, postural hypotension, and decreased blood pressure.[17] Some of UARS patients tend to report light-headedness and fainting following abrupt standing.[9]

Table 1. Differences in clinical features between UARS and OSA[3]

Clinical Features	Upper Airway Resistance Syndrome	Obstructive Sleep Apnea
Male: Female ratio	1:1	2:1
Age	All ages	Post-menopausal women Male >40 years old Children
Sleep onset	Insomnia	Fast
Daytime symptoms	Fatigue Tiredness	Sleepiness (less frequent in children)
Snoring	Common, may be absent	Almost always
Apnea	No	Common
Somatic functional complaints	Chronic pains, headaches, fibromyalgia	Rare
Orthostatic symptoms	Dizziness, fainting, cold hands/feet	Rare
Body habitus	Normal or Slim	Obese
Neck circumference	Normal	Large
Blood pressure	Normal or Low	High

In terms of clinical assessment, it is considered important to evaluate the anatomical features of the nose, maxilla, mandible, and soft tissues as several craniofacial traits have been observed to be unique to UARS. These patients have the characteristic long-face syndrome, which includes a small and narrow chin and a narrowed mouth opening. Other craniofacial abnormalities include a long uvula, low soft palate, and increased overbites.

When opening the temporomandibular articulation, typically a 'click' and a subluxation are present and may be palpated. The mandible is positioned at the back with a high and narrow palate.[9,10]

Finally, Guilleminault et al reported that one-fifth of UARS patients exhibit low resting arterial blood pressure or orthostatic intolerance. In highly obese young individuals, UARS should also be explored.[9,10]

DIAGNOSIS

Patients suspected of having sleep-disordered breathing and their companions in bed should be assessed in a complete history taking, paying special attention to sleep cycles, symptoms during the daytime, the development and progression of nocturnal symptoms, aggravating factors, family history, comorbidities, so on. Body mass index (BMI), neck circumference, passageways of nasal, and oropharyngeal area existence of micrognathia, retrognathia, macroglossia, and other palate abnormalities—all anatomic variables important in the development of obstructive sleep-disordered breathing—are all assessed during a focused physical examination.[1]

The presence of supporting clinical presentation as described above, as well as the accompanying positive diagnostic findings, is required for the diagnosis of UARS. Several diagnostic tools are utilized in diagnosing UARS, including polysomnography (PSG), Esophageal

manometry (Pes), and Electroencephalography (EEG).[5]

Polysomnography

The most important criterion of PSG for Upper Airway Resistance Syndrome is the non-existence of PSG fulfilling criteria for OSA. PSG results of UARS patients display events indicating partial upper airway obstruction, such as increased respiratory effort, the presence of RERAs, and airflow restriction. As previously stated, there is no quantitative criteria for these occurrences in the diagnosis of UARS.[17]

Polysomnography (PSG) findings in UARS are described as:

a. The presence of RERA events, which are currently defined by The American Academy of Sleep Medicine (AASM) as a sequence of breaths with increased respiratory effort identified by the flattening of the airflow curve of the nasal pressure cannula, which leads to awakening/arousal and does not meet the criterion for hypopnea and apnea. RERAs have a 10-second duration.[17]
b. Normal AHI score (AHI <5), with no significant hypopnea or apnea found.
c. No remarkable desaturation of oxygen.
d. Limitation of airflow during sleep was noticeable. The definition of airflow limitation is a rise in respiratory effort in the absence of a comparable increase in airflow. Limitation of airflow manifests as a flat line appearance in contrast with the curve of normal breath which usually looks bell-shaped, with a 2 to 29% decrease in amplitude compared to normal breaths.[5,9] Airflow restriction is related to the increased effort of respiration, furthermore, in PSG, this condition has been employed as an indirect sign of increased upper airway resistance. For RERAs, a nasal cannula or pressure transducer is considered more reliable in terms of detecting breathing variations and identifying air flow restrictions compared to a thermistor. RERAs is a term established by AASM to point out events where arousals happened due to airflow limitation). As a result, instead of esophageal manometry, the nasal pressure cannula may be utilized to identify RERA-type episodes.[9]

The term RERA was created by the AASM task group on sleep-related breathing problems to characterize arousal events linked to the increase of respiratory effort. The incident needs to meet the requirement to be defined as an abnormal breathing pattern, which is interpreted as a gradually increasing negative pressure of the esophagus or a respiratory curve that becomes flat which lasts for more than ten seconds and results in arousal.[9]

Esophageal Manometry (Pes)

Esophageal manometry is still considered as the gold standard in diagnosing UARS. The tool functions to measure distal esophageal pressure, often known as Pes. In UARS patients, three abnormal patterns are expected:

a. "Pes crescendo" is interpreted as an escalating increase of negative peak inspiratory pressure during every

breath which ends with arousal seen in an electroencephalogram (EEG).

b. "Sustained constant effort of respiration"; the tracing of Pes exhibits a consistently abnormal negative peak inspiratory pressure which differs from the normal standard pressure and exists for more than four breaths, sometimes longer than one minute.
c. Pes reversal is described as an ending of both events above and also defined as a reduction of respiratory effort manifested as less negative peak inspiratory pressure, frequently not accompanied by EEG arousal.[3]

One of the earliest signs of respiratory arousal is decreased esophageal pressure (Pes) as a result of increased resistance of the upper airway. However, many laboratories do not utilize this approach since it disrupts sleep quality, is not well-accepted by patients, and is considered as aggressive procedure.[18]

A large amount of respiratory effort as UARS patients are asleep can be seen using esophageal pressure monitoring. Esophageal pressure monitoring remains held as the gold standard in diagnosing Upper Airway Resistance Syndrome. To make the procedure more tolerable for adults, it is recommended to put in a pediatric feeding catheter to use rather than a balloon catheter.[9]

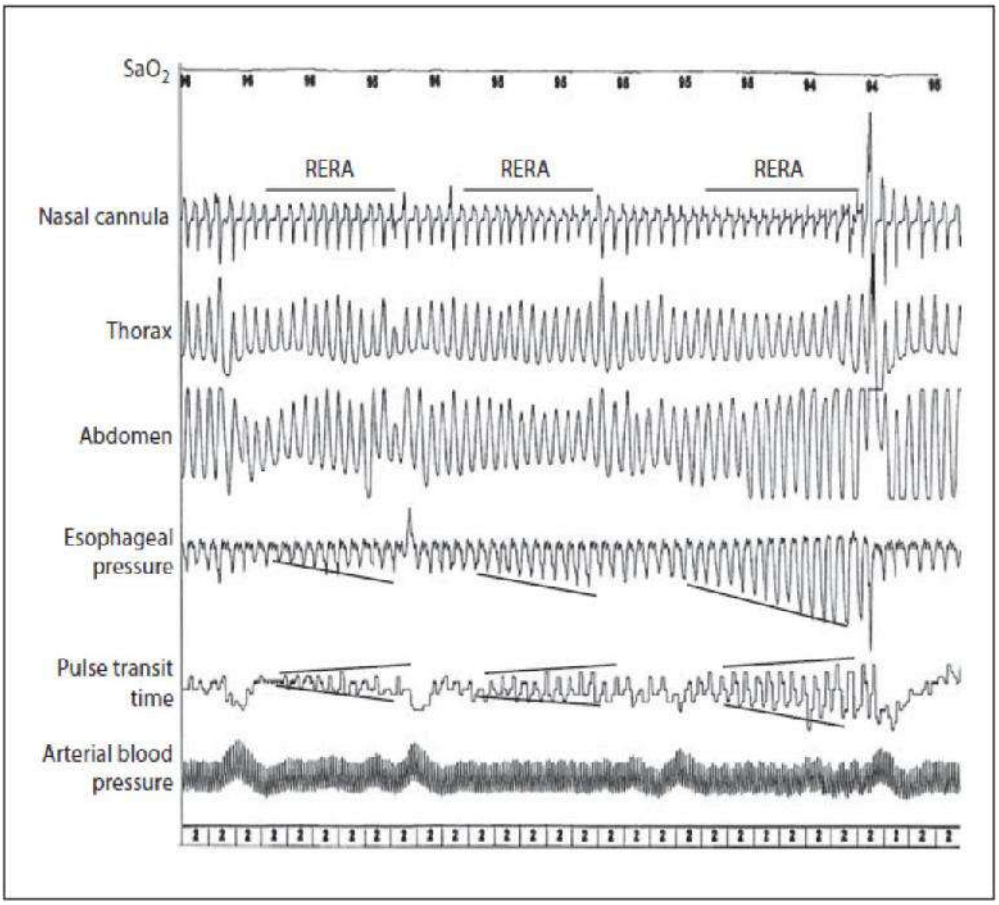

Figure. 2. A typical pattern of RERAs throughout sleep study. The illustration demonstrates the repetitive occurrence of RERAs along with an escalating limitation of airflow detected by nasal cannula, leading to an rise in respiratory effort (both pulse transit time and esophageal pressure). These episodes tend to lead to both sleep fragmentation as well as an increase in arterial blood pressure[10]

Electroencephalogram (EEG)

Upper Airway Resistance syndrome is associated with sleep fragmentation. According to the established criteria of AASM15, sleep fragmentation may be suggested by a surge in awakenings defined by rapid frequencies of EEG.[17] EEG in UARS patients identified larger quantities of alpha frequency. During NREM sleep, UARS patients exhibit greater theta and low alpha powers (7-9 Hz) and greater power of delta throughout REM sleep. Escalating activity of delta frequency prior to the reversal of Pes, as well as the rise of other frequencies after the event, show that major alterations of EEG occur with Pes episodes that do not result in observable EEG arousal.[3]

Alpha-frequency central lead EEG is more prominent in UARS patients than OSA patients. According to certain studies, people with OSA and UARS have different cortical responses to changes in breathing patterns while they are sleeping.[19] The increasing amount of short EEG arousals following episodes of airflow limitation during inspiration suggest an effort to avoid collapsing upper airway (UA). Patients with UARS maintain this upper airway protection system, whereas OSA patients have significant deficits.[2]

More sensitive approaches, such as analysis of cyclic alternating pattern analysis (CAP) on EEG, have been proposed. CAP is defined as a well-described non-REM sleep pattern characterized by periodic electrocortical events which are distinctive from the background EEG activity. Slow-wave sleep awakenings, EEG synchronization with K-complex, and delta waves are all included in CAP.[17]

In addition to central nervous system hyperactivity, a rise in CAP frequency implies sleep fragmentation and instability. Patients with UARS may demonstrate instability of the sleep stage. This instability may be identified by the frequent transition from a deeper to a lighter stage of sleep which later ends with wakefulness. The characterized decreases in sleep depth can be described as follows: REM, N3, N2, N1, and wakefulness.[4] The CAP rate has been linked to daytime drowsiness and weariness.[3] The CAP analysis revealed a connection between sleepiness and fatigue measures in UARS patients.[17]

PAP titration method

Diagnosing UARS is difficult as a consequence of the following factors: Measurement of esophageal pressure is an intrusive procedure many individuals find difficult to bear. There is no limit to the number of RERAs that can be used to explain UARS diagnosis using polysomnography.[18]

Furthermore, there have been no procedures to measure excessive daytime sleepiness (EDS) objectively. However, it is concluded that a rise in upper airway resistance is considered as a pathological condition. The result of PSG which shows no hypopnea/apnea events, nor lowered oxygen saturation, but an increase in upper airway resistance may guide us to diagnose Upper Airway Resistance Syndrome. A healthy person's upper respiratory tract

pressure normally does not transcend over 4 cmH2O. Currently, the most objective non-invasive approach for determining upper airway resistance is by PAP titration.[18]

PAP therapy is now a treatment with the highest effectiveness to overcome upper airway resistance. PAP treatment dramatically alleviated neuropsychiatric symptoms, and EDS was demonstrated to diminish. Among the minor diagnostic criteria is the demonstration of improvement in EDS after PAP treatment. PAP titration is the initial test performed on individuals who will be treated with PAP. The pressure obtained during PAP titration is the pressure required to maintain the patient's upper airway intact and open. PAP titration allows us to identify the precise amount of pressure required for our patients.[18]

As mentioned above, there are two things to keep in mind when performing PAP titration on patients suspected of Upper Airway Resistance Syndrome. The first thing is, an observed pressure beyond 4 cmH2O during PAP titration may confirm the presence of upper airway resistance. Second, this observation can also be used to determine the pressure deemed necessary to treat UARS.[18]

COMPLICATIONS

Patients with UARS are more likely than those with OSA to experience persistent insomnia, excessive daytime sleepiness, and exhaustion, while OSA patients display abnormalities of the upper airway with more severity which leads to a pharyngeal collapse in comparison to patients with UARS.[2,7]

Both excessive daytime sleepiness (EDS) and exhaustion are the most incapacitating manifestations of sleep-related breathing disorders. It may induce a lower quality of life, and also a higher incidence of road and work-related accidents. Even with adequate sleep, EDS and tiredness are the most frequent complaints of Upper Airway Resistance Syndrome patients. The majority of patients report a lack of restful sleep, fatigue, and trouble in doing daily tasks.[2,7]

A research compared the health-related quality of life (HRQoL) of UARS and OSA patients with the general population. OSA and UARS have equivalent impacts on HRQoL across disease categories, although they are notably worse when compared to the effects in the general population. Muscle discomfort, obesity, female sex, depression, and the use of psychiatric drugs all had a negative impact on HRQoL in UARS patients.[20]

Another research found that, compared to mild OSA patients, patients with UARS experienced more exhaustion and lower sleep quality (respectively p 0.05 and P=0.003), and also showed higher scores on both of Beck inventories compared to the "control group" (P=0.02). In conclusion, when compared to mild OSA, patients with UARS often experience worse quality of sleep, greater exhaustion, and poorer early morning sustained attention.[2]

UARS patients have been observed to have poorer quality of sleep, higher level of

attention disturbances and fatigue, indicating disrupted pattern of sleep. Furthermore, some researchers have shown that UARS increases the likelihood of arterial hypertension that is resistant to treatment due to sympathetic overactivity. These events could indirectly raise the risk of developing stroke.[21]

THERAPY

To avoid those aforementioned complications, UARS patients should receive effective therapy. There are several therapy studies in the literature, although the majority of them are based on case series or case reports. Continuous positive airway pressure through the nasal (CPAP) has been investigated as a treatment for UARS, and current studies demonstrate that it can relieve a number of symptoms of the condition.[16]

Other treatments considered were the use of oral appliances, surgeries of the nasal and palate, and advancement of t maxillomandibular. Weight loss and positional therapy were also deemed to give a positive impact. Long-term research to assess therapy response will be beneficial in properly defining this SBD.[16]

CPAP Therapy

The most recommended treatment for UARS is CPAP (Continuous positive airway pressure) therapy. The use of CPAP therapy reduces transient arousals, increases sleep latency at MSLT, and also increases the proportion of NREM phases 3 and 4.[16]

Early investigations reported positive responses to CPAP therapy. Daytime sleepiness, weariness, and snoring may also lessen following CPAP therapy.[3] Nonetheless, in several studies, patients' excessive daytime drowsiness and tiredness did not improve with CPAP treatment. As a result of the absence of positive benefits, some patients did not comply with CPAP resulting in low compliance and adherence.[16]

In regard to CPAP titration, a similar protocol used for treating OSA is recommended. Following ideal CPAP, at the end of inspiration, the esophageal peak pressure must be higher than -7 cm H2O and displays RERA index below 10. If this is unable to be achieved, an empirical pressure level of between 8 and 10 cmH2O may be applied for the CPAP.[7]

Oral Appliances

UARS patients have a narrow and small area of the posterior airway behind the tongue’s base. Oral appliances shift the mandible and tongue forward to widen the oropharyngeal airway and relieve obstruction in the oropharynx.[3,17] Oral appliance therapy (OAT), particularly Mandibular Advancement Devices (MAD), which kept the mandible protruding during sleep (expanding the retro-glossal space), has been demonstrated to be helpful. Patients with UARS are suitable candidates for the OAT (MAD) because their threshold for arousal is lower and their muscle’s responsiveness is better, resulting in lower pharyngeal collapsibility (lower Pcrit).[22]

The adverse effects of using oral devices, such as increased salivation as well as temporary soreness of teeth, were mild and manageable, with no crucial consequences. During a lengthier follow-up, both subjective and objective components of the response following therapy were examined. The findings revealed that the use of an oral appliance was beneficial in reducing fragmentation of sleep, as well as subjective and objective daytime sleepiness.[16] In UARS patients, OA treatment has been demonstrated to lower negative esophageal pressure, reduce the awakening index, raise percentage of sleep efficiency and minimum saturation of oxygen, in addition to decrease subjective EDS and snoring.[17]

Surgical Management

Surgery may be considered in UARS patients with low compliance and intolerant to CPAP therapy or who have not shown significant improvement following CPAP therapy. The goal of surgical treatment for UARS is to address the underlying anatomical anomalies of the upper airways such as nasal allergies treatment, nasal surgeries (turbinate reduction, septoplasty), palatal soft-tissue surgeries (soft palate ablation using radiofrequency, uvulopharyngoplasty, etc.), advancement of genioglossus, orthognathic surgery (advancement of maxillary mandibular).[3,16]

The most regularly performed surgeries which is considered successful in treating UARS are laser-assisted Uvulopalatopharyngoplasty (LAUP) surgery and Uvulopalatopharyngoplasty (UPPP) surgery. The cost of LAUP method is considered more affordable and effective.[5]

Riley et al presented a multilevel strategy of pharyngeal surgeries which includes UPPP, osteotomy of mandibular with the advancement of genioglossus (GA), followed by Hyoid myotomy with advancement (HM). A 60-65% postoperative success rate and a result comparable to CPAP therapy were reported. Septoplasty in addition to resection of bilateral inferior turbinate must be retained only as an addition to surgery of the pharynx or in order to increase CPAP tolerance.[5]

CONCLUSION

Upper Airway Restrictive Syndrome (UARS) is included as one of sleep-related breathing disorder. UARS is a term specified to clinical symptoms experienced by patients with unexplained excessive daytime sleepiness in the setting of PSG that doesn't fulfill the criteria of OSA (as interpreted by an AHI of <5 events/hour), but exhibits recurrent arousals (sleep fragmentation) due to elevated upper airway resistance. UARS may result in great impairment of both sleep quality and QoL (quality of life). Despite being acknowledged in medical practice, UARS remains underdiagnosed and undertreated. Therefore, it is critical for the health professional to understand the diagnosis and suitable treatment for UARS. Further studies are deemed necessary to confirm significant outcomes and effective

management in order to establish UARS in sleep medicine.

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