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ORIGINAL ARTICLE

Descriptive Study: Level of Communities Knowledge And Perception About Tuberculosis (TB) in Denpasar, Bali

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ABSTRACT

Background: Success rate of Indonesia Tuberculosis (TB) treatment did not evenly distribute to every province in 2016, although various program had been carried out by Indonesia Government. Bali's Case Notification Rate (CNR) and Success Rate (SR) of TB also did not reach target in 2017. Successful control of TB can be influenced by community's level of knowledge and perception about TB. Our research objective was to know communities level of knowledge and perception about TB in Denpasar, Bali.

Method: This was cross-sectional research. Our sample was Denpasar communities who visited Puputan Renon Field Car Free Day (CFD) at 25 March 2018. Sample was chosen by consecutive sampling.

Results: Our research result was almost (62%) of respondent had poor knowledge about TB and 67% respondent had right perception about TB.

Conclusion: We can conclude that Denpasar communities had poor level of knowledge and good perception about TB.

Keywords: Tuberculosis; Level of Knowledge; Perception

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by infection with the bacteria Mycobacterium tuberculosis. The clinical manifestations of TB are dominated by respiratory complaints due to bacterial tuberculosis infection in the lungs. Other clinical manifestations can include enlarged lymph nodes, pain in the spine, and skin nodules caused by extra-pulmonary TB infection.[1] Transmission of TB bacteria occurs through droplets excreted by TB patients when coughing or sneezing.[2]

Today, the TB prevalence rate in the world is still high. In 2016, the World Health Organization (WHO) found that TB is one of the top 10 causes of death globally. Based on WHO's data, in 2016, there were 10.4 million TB sufferers in the world, with an estimated 1 million of them being children. The TB mortality rate in the world in 2016 reached 1.7 million adults and 250,000 children. India, Indonesia, and China are the top three countries with the highest TB prevalence rate globally, where 64% of TB sufferers are in these countries. This fact shows that Indonesia still has many TB sufferers, especially pulmonary TB, compared to other countries in the world.[3]

In Indonesia, there has been a decrease in TB prevalence rate by 50% from 1990 to 2015, with an estimate that more than 50% of cases are individuals aged over 15 years. The quality of the process from finding to diagnosis and the sensitivity of determining the criteria for suspicion also showed a positive development reflected in the increase in the proportion of confirmed pulmonary TB cases. The proportion of confirmed TB cases has increased significantly from 1999, namely 7% reaching 14% in 2015.[4]

A different thing is seen in the success rate of TB treatment in Indonesia. There is a significant difference in numbers between regions, unequal distribution of successful TB treatment. The increase in the incidence of drug-resistant TB in Indonesia is also related to the success of TB therapy.[4] Nationally, the success rate of TB treatment in Indonesia is 84%, with the highest achievement of 93% in North Sulawesi province and the lowest in Central Kalimantan, 37%.[5]

Case Notification Rate (CNR) and *Success Rate* (SR) are indicators used as benchmarks for TB control in Indonesia. CNR shows the total number of TB patients found and recorded among the 100,000 population, and SR is an indicator showing TB treatment's success. During the past three years, there has been an increase in the CNR of Bali Province to 75/100.000

population in 2016, but this figure has not met the targeted CNR of 78/100.000.[6]

In 2016, Denpasar's city had the highest CNR rate in Bali at 130, 39 per 100.000 population. The SR figure for Bali Province has also not met the 2016 Strategic Plan for the Health Service and the Ministry of Health. Based on data obtained by the Bali Provincial Health Office in 2017, the achievement of the SR Bali Province in 2016 was only 55.12%, with the target of the Health Office's Strategic Plan 86% and the Ministry of Health 83%. Denpasar is the city/district with the lowest SR rate in Bali, namely 35.62%.[7]

The low achievement of the SR with CNR in Denpasar City can be caused by various government and community factors. Government factors relate to promotive, preventive, and curative efforts carried out by the Public Health Center or hospitals. In contrast, community factors include knowledge and perceptions, which then influence people's behavior in dealing with TB infection, especially adherence to treatment.[8]

One of the studies conducted by Pasek et al regarding the relationship between perceptions and knowledge levels of tuberculosis patients with medication adherence in the work area of Buleleng I Public Health Center found that patients with positive perceptions and a good level of knowledge about TB had a 25% greater likelihood of adhering to treatment than patients with the opposite.[8] In research conducted by Zaenal S also obtained similar results.[9]

All the facts above indicate the importance of researching public knowledge and perceptions about TB. This study was conducted to know public knowledge and perception about TB, especially in Denpasar, Bali. The research results will later become material for evaluation and consideration of TB control program planning in Denpasar City in particular and Indonesia in general.

METHOD

This research was conducted at Puputan Renon Field, Denpasar, on the Car Free Day (CFD) activity on Sunday, March 25th, 2018. This research is descriptive quantitative with a cross-sectional approach. The study population was all CFD participants at Renon Field on Sunday, March 25th, 2018. The inclusion criteria were CFD participants who were domiciled in Denpasar City with the exclusion criteria of participants who refused to fill out a questionnaire and did not read and write fluently. The number of respondents in this study was 100

people. Sampling was done using *consecutive sampling.* Data collection was carried out by distributing questionnaires. *Informed consent* was carried out to determine the availability of respondents filling out the questionnaire. The collected data is then processed using quantitative statistical *software*.

RESULT

The number of respondents in this research are 100 people, with the percentage of men 43%, and women 57%.

Table 1. Characteristics of Research Subjects

Variable	%
Gender:	
Male	43%
Female	57%
Age:	
Productive Age (15-64 years)	96%
Unproductive age (<15 years or> 64 years)	4%
Last Education	
Elementary School	3%
Junior High School	7%
Senior High School	41%
College	49%
Profession	
Working	62%
Does not working	38%
Income	
Rp 0,00- Rp 2.363.000,00	56%
>Rp 2.363.000,00	44%

Respondents' ages were grouped by productivity, where respondents aged 15-64 were included in the productive age category, and respondents aged <15 or <64 were included in the unproductive age criteria. The respondents in this study are dominated by the workers (62%) and income according to or below the Minimum Wage Districts/Cities (UMK) Denpasar (56%) (Table 1).

Table 2. Respondents' Knowledge Level of TB

Knowledge level	Total (%)
Good	38 (38%)
Less	62 (62%)

Table 3. Respondents' Knowledge Level of TB based on Gender, Age Group, Education Level, Occupation, and Income

Variable	Knowledge Level	
	Good	Less
Gender		
Male	13 (30.2%)	30 (69.8%)
Female	25 (43.9%)	32 (56.1%)
Age		
Productive Age	38 (39.6%)	58 (60.4%)
Unproductive Age	0 (0%)	4 (100.0%)
Education		
Elementary-Junior High School	0 (0.0%)	10 (100.0%)
Senior High School-College	38 (42.2%)	52 (57.8%)
Profession		
Working	21(33.9%)	41 (66.1%)
Does not working	17 (44.7%)	21 (55.3%)
Income		
≤Rp 2.300.000,00	21 (37.5%)	35 (62.5%)
>Rp 2.300.000,00	17 (38.6%)	27 (61.4%)

In this study, the average value of respondents' knowledge about TB was

9.6 with a maximum score of 14 and a minimum score of 3. Through the normality test the data obtained the distribution of the total data of the respondent's knowledge value is not normal, so the number used as the cutting point of the knowledge level determination is the median total knowledge value. Respondents with a value of %10 are grouped as respondents with good knowledge and respondents with a value ≤ 10 are grouped as less knowledgeable respondents. Respondents' knowledge of TB in general, can be seen in Table 2.

Table 4.Categories of Respond Perceptions of TB

Categories of Respond	Total (%)
Positive	67 (67)
Negative	33(33)

In this study, the average respondent's perception of TB was 8.7, with a maximum score of 10 and a minimum score of 2. After the normality test, it is obtaining that the distribution of the respondent's perception value data is abnormal, so the cut point of the value to determine the respondent category is the median data (9.00).

Respondents with a perceived value of > 9 were grouped as respondents with positive perceptions, while respondents with a value ≤ 9 grouped as respondents with negative perceptions. Respondents' perception of TB in general, can be seen in Table 4.

Table 5. Categories of Respondents' Perception of TB based on Gender, Age Group, Education Level, Occupation, and Income

Variable	Categories of Respond	
	Positive	Negative
Gender		
Male	28 (65.1%)	15 (34.9%)
Female	39 (68.4%)	18 (31.6%)
Age		
Productive Age	67 (69.6%)	29 (30.2%)
Unproductive Age	0 (0.0%)	4 (100%)
Education		
Elementary-Junior High School	2 (20%)	8 (80%)
Senior High School-College	65 (72.2%)	25 (27.8%)
Profession		
Working	46 (74.2%)	16 (25.8%)
Does not working	21 (55.3%)	17 (44.7%)
Income		
≤Rp 2.300.000,00	34 (58.9%)	10 (41.1%)
>Rp 2.300.000,00	27 (77.3%)	17 (22.7%)

Table 6 showed that the percentage of respondents' answers to each perception statement in the research form. All statements of perception are dominantly answered correctly by the respondents. The two statements with the percentage of the wrong perception, the highest in the statement, "TB is a disease that embarrassing" (32%) and "TB Treatment should be discontinuing if complaints had improved" (25%).

Table 6. Percentage of Perception Category based on Statement on Research Form

Statement	Perception	
	Positive	Negative
TB is an embarrassing disease	68 (68%)	32 (32%)
TB patients must be isolated away from society to prevent contagion.	82 (82%)	18 (18%)
I checked myself into the public health center when I had a cough complaint for more than 2 weeks with fever.	96 (96%)	4 (4%)
If I have a cough for more than 2 weeks, I would rather buy medication at the pharmacy than check myself into a health facility.	87 (87%)	13 (13%)
I don't need to know information about TB	93 (93%)	7 (7%)
Providing TB information to the public is not necessary.	93 (93%)	7 (7%)
TB is an incurable disease	89 (89%)	11 (11%)
If there are families or people in the neighbourhood are experiencing cough complaints more than 2 weeks with fever, you would advise them to check with the health facility.	95 (95%)	5 (5%)
Health checks are not important.	95 (95%)	5 (5%)
TB treatment should be discontinued if complaints are already improved	72 (72%)	28(28%)

DISCUSSION

Research on knowledge levels found that 38% of respondents had good knowledge, and 62% had less knowledge of TB. Other studies on TB knowledge levels have mixed results. The research conducted by Sandha et al. on the level of knowledge and category of people's perception of Kecicang Karangasem Village against TB got similar results to this study, namely dominant (55.1%) respondents have less knowledge of TB.[10]

Research conducted by Rahman et al. on TB knowledge in the working area community of Selan Subordinate Health Center, South Kalimantan, also received 50% of respondents who had less knowledge about TB and only 20% of respondents who had good knowledge.[11] In qualitative research conducted by Friskarini et al. regarding adolescents' knowledge and attitude (15-20 years), Tangerang District on TB got the results most teenagers expressed no idea when asked about the symptoms and causes of TB disease.[12]

Research conducted by Pasek et al. regarding the knowledge community in the working area of the Buleleng 1 health center regarding TB got different results. The study found dominant respondents (67.5%) have good knowledge of TB and only 32.5% have less knowledge about TB.[8] Research by Siswanto et al. with the population of community respondents in the working area of public health center of Andalas, Padang got 69.2% of respondents had good knowledge of TB.[13]

The difference in results obtained in some of these studies can be caused by various factors, such as differences in the research methods and characteristics of the respondents used. The research method section consists of the place and time of the research, the design of the research, the size of the sample, the sampling technique, the data collection technique, and the analysis of the data. The research site is part of a research method that clearly looks at the differences in the articles mentioned above. Each region has a diverse level of TB knowledge, where there are areas with dominant communities with good TB knowledge and vice versa.[14]

It gives an idea that there is a gap in people's knowledge levels in some regions of Indonesia regarding TB. Most of the above research are cross-sectional designs, but there are differences in sample size and sampling techniques. The sample size in the research mentioned above varies. The sample size affects the bias obtained in the results of the study and the suitability of the results of the study to the reality in the field.[14]

So, the difference in the study results in some of these studies can be caused by bias due to the small size of the sample and the difference in characteristics of the respondents used. The characteristics of respondents can also affect the level of knowledge. According to Notoatmojo, the level of knowledge can be influenced by community characteristics such as education level, occupation, and age.[14]

This research has been conducted on data analysis level of knowledge by gender, age group, education level, occupation, and income shown in table 4. There was no difference in the distribution of knowledge levels based on gender, age, education, employment, and income in this study.

Research by Sandha et al found a difference in the distribution of TB knowledge levels based on age, education, and employment. Respondents of unproductive age, dominant (66.7%) have less knowledge of TB, while productive age respondents, dominant (54.3%), have

a good knowledge of TB. Respondents who have a background in the study of elementary and junior high school education and respondents who do not work dominantly have less knowledge about TB. Respondents with a background of high school education, college, and work dominantly have a good knowledge of TB. Research conducted by Selleca in 2012 showed that a relationship of economic status (income) with TB knowledge levels and delays in TB diagnosis.[10,15]

According to Notoatmodjo, age is one of the factors that can influence knowledge. This is related to changes in psychological aspects and maturity of thinking with age, thus affecting the ability to capture and process information. The level of education is also an essential factor that can affect knowledge. According to Notoatmojo, the higher the level of individual education, it will be easier for the individual to receive and develop the information or knowledge received. Employment and economic status are two things that are related and can affect knowledge levels.[14]

Employment and economic status can affect the process of accessing information and exposure to dominant information in individuals. Individuals who work logically will get easier exposure to information than individuals who don't work. Individuals working in the health field will have a better level of health knowledge than individuals who do not work in health areas related to information exposure. In this study, there was no difference in the distribution of knowledge levels based on age, education level, occupation, and income due to the number of different respondents in each group and there were groups with fewer than ten respondents.

Low levels of community TB knowledge can affect the success of TB prevention in an area. The success of TB treatment is influenced by a variety of factors, such as preventive measures of TB transmission, speed of diagnosis, and successful treatment. Preventive measures on TB can be optimized if the public knows and understands about TB transmission patterns. The speed and accuracy of diagnosis can also be influenced by the level of knowledge of the community. In the study conducted by Selleca, it was found patients with low TB knowledge levels also had an average delay in first visits to primary health facilities of 128.84 days compared to patients with high TB knowledge.[15]

The drug-taking adherence of TB patients strongly influences the success of TB treatment. The level of knowledge can also affect the

compliance of the patient's treatment. In the study conducted by Siswanto et al. obtained the level of patient knowledge about TB significantly related (p=0,000) to the level of treatment compliance. TB patients with an adequate level of knowledge have a good level of compliance, and vice versa. In the study also obtained, in addition to the level of knowledge, family support also influenced the patient's compliance in undergoing treatment.[13]

Other studies conducted by Muture et al. in the population in Nairobi Province, Kenya through multivariate analysis obtained, significantly less knowledge of TB (OR 8.67%; 95% CI 1.47-51.3) compliance affected the drug-taking of TB patients.[16] Research conducted by Paixao et al. in populations in southeastern Brazil found that the quality and quantity of information about TB disease held by respondents was related to drop out cases in TB patients. In the study, patients with fewer details about TB had a higher risk of drop out than patients with good information about TB.[17] Research by Vijay et al. in India also gained through poor knowledge that TB affects the treatment compliance of TB sufferers with AOR-1.88 (1.35-2.63).[18]

The facts above can provide an overview of the causes of CNR and SR Bali that have not reached the target in 2016. The low level of public knowledge can affect various aspects of TB management process, especially in Bali. The increase in knowledge about TB can be done by providing information about TB to the public.

Based on qualitative research conducted, Friskarini et al., the majority of respondents did not know the ways of transmission of TB and prevention of TB. Most of the respondents said transmission of TB due to a virus and can be transmitted through glass or plate that is used together with TB patients. The study also found that most respondents had low knowledge of TB symptoms. The dominant respondent said coughing up blood as a symptom of TB, while other TB symptoms were unknown.[11]

In the study by Sandha et al. got similar results. The dominant respondents had less knowledge about the risk factors and causes of TB as well as TB prevention. This fact can be due to the incomplete provision of information about TB to the public.[10]

The results of public perception research on TB found that 67% of respondents had a positive perception of TB, and 33% had a negative perception of TB. Different perception

categories of gender, age group, education level, occupation, and income can be seen in table 7. Respondents with an unproductive age all had negative perception categories of TB, while respondents with the dominant productive age had a positive perception of TB (69.6%). Respondents with the background of the study of dominant elementary and junior high schools had negative perceptions of TB (80%). In comparison, respondents with the background of the study of senior high school and college dominantly had a positive perception of TB (72.2%).

Other studies on public perceptions of TB have had mixed results. Research conducted by Sandha et al. in Kecicang Village, Karangasem, found that most respondents (67.3%) had positive perceptions about TB. In this study, there was no difference in the distribution of perception categories based on the respondent's age, education level, occupation, and respondent's income.[10] Another study conducted by Pasek et al. In 2013, in Buleleng 1 Public Health Center's work area, found that 82.5% of respondents had positive perceptions about TB.[8]

The qualitative research conducted by Friskarini et al. on adolescents aged 15-20 years in Tangerang District obtained different results. In this study, most of the informants believed that pulmonary TB was not a dangerous disease, which in turn could affect the emergence of a lack of care about pulmonary TB disease.[12] Qualitative research conducted by the Media in Sungai Tarab District, Tanah Datar Regency, West Sumatra Province, found that most respondents had the wrong perception about TB. In the Focus Group Discussion (FGD) activity conducted, most respondents believed that TB is a disease caused by black magic and heredity. Most informants also thought that TB symptoms were commonplace and did not require particular therapy, making it late for them to go to health services.[19]

The facts above show different categories of public perceptions about TB in several regions in Indonesia. There are several areas with community dominance that have negative perceptions about TB. Public perception can influence the success of TB control programs, especially in Indonesia. One of TB management's essential factors that can be influenced by public perceptions complies with TB patients' medication. In a study conducted by Putera et al. On a population in the Province of East Nusa Tenggara (NTT), it was found that knowledge and perceptions influenced

TB patient medication adherence. In the multivariate analysis, only people's perceptions of TB significantly affected TB patient medication adherence with OR (95% confidence interval (CI)) 4.75 (2.30-9.86) p <0.001, while for demographic characteristics and knowledge about TB did not have a significant effect.[20]

Research conducted by Pasek et al. found that patients with positive perceptions of TB were 21.41 times more likely to adhere to treatment with p = 0.018 than patients with negative perceptions. In another study, it was stated that apart from knowledge and perceptions of TB, alcoholism, expensive health facilities, the presence of a family with TB, age and marital status, and monthly income were related to TB treatment adherence.[8]

In a study conducted by Sandha et al., the perception statement in the form of "TB is a shameful disease" is the dominant statement answered with respondents' negative perceptions. Other statements that were predominantly answered with negative perceptions by respondents were statements about the respondent's awareness of having a complaint and the cost of TB examination at the Public Health Center and hospitals, classified as expensive. This fact can illustrate the low achievement figures for the CNR and SR, especially in Bali.[10] CNR and SR were influenced by patient arrival for self-examination and adherence to medication. If most people still believe that TB is an embarrassing disease, TB drugs can be stopped when complaints improve. Delays in checking into health services, the risk of late diagnosis, disease transmission, treatment non-compliance, and drug resistance is high.

In several studies, it was said that there was a relationship between the level of knowledge and public perceptions of TB. Therefore, one of the actions that can change negative perceptions into positive ones is to increase knowledge. In a study conducted by Putra et al., it was stated that the cause of the low individual's knowledge of TB was the absence of a family history of TB and never reading or attending TB education activities.[20]

Therefore, providing information about TB to the broader community is one method that can be used to increase public knowledge and perceptions about TB. Education and personal provision of information by health workers to TB patients and their families is also a way to increase public knowledge and perceptions about TB.

This study's weakness is because the researcher does have no data on the history of exposure to TB

information on the respondent, which consists of information media and TB information material that has been obtained. The relationship between knowledge, perception, and the history of receiving information about TB in the respondent is not known. The researcher has not divided the respondent's level of knowledge based on the type of question in the questionnaire, not to know which the respondent does not understand the category of TB information.

CONCLUSION

In this study, it was found that 38% of respondents had good knowledge, and 62% of respondents had less knowledge about TB. There were no differences in the distribution of knowledge levels based on age, sex, education level, occupation, and income.

The category of respondents' perceptions of TB was dominant. It was found that 67% of respondents had positive perceptions about TB, and 33% of respondents had negative perceptions. All non-productive (100%) respondents have negative perceptions of TB, while the dominant respondents of productive age (69.6%) have positive perceptions about TB. Respondents with a dominant Elementary-Junior High School education level (80%) had a negative perception of TB. In comparison, respondents with a dominant Senior High School-College education level (72.2%) had a positive perception of TB.

Suggestions for further research are researching public knowledge and TB perceptions with more comprehensive area coverage and sample size. Further research is needed on the factors that influence the level of knowledge and public perceptions about TB, including the effect of providing information on knowledge. Further research is needed on the factors that influence the success of TB control, especially in Indonesia.

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ORIGINAL ARTICLE

Two-years Biannual Evaluation of Drug-resistant Tuberculosis Patients Completing Their Treatment at Persahabatan General Hospital Jakarta

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ABSTRACT

Background: Drug-resistant tuberculosis (DR-TB) is a worldwide threat, including in Indonesia, which course of treatments are time consuming and are expensive. Recent findings suggest trends in recurrence of DR-TB, while no data is available to summarize the recurrence of DR-TB in Indonesia. This study aimed to evaluate DR-TB patients which was biannually performed for two-years (e.g. at the 6th, 12th, 18th, and 24th mos) after treatment completion.

Methods: This cross-sectional study involved DR-TB patients completing their treatment at Persahabatan General Hospital Jakarta, Indonesia, between April and December 2017. The post-treatment evaluation during the 6th, 12th, 18th, and 24th mos included clinical, chest x-ray (CXR) and sputum culture examination.

Results: Sixty patients were observed in this study, 31 (51.7%) were males and 29 (48.3%) were females. The mean age was 42.3$\pm$12.5 yo and the mean body mass index was 21.75$\pm$4.34. Fourty nine (81.7%) patients showed extensive lesions per CXR and none of the patient showed *Mycobacterium tuberculosis* growth per sputum culture.

Conclusion: There was no recurrence of DR-TB from patients completing their treatment at Persahabatan General Hospital Jakarta, Indonesia during two-years post-treatment evaluation.

Keywords: drug-resistant tuberculosis evaluation, drug-resistant tuberculosis recurrence, radiological and microbiological tuberculosis evaluation

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INTRODUCTION

Globally in 2017, it is estimated that the incidence of tuberculosis (TB) cases are 10 million (9.0-1 1.1 million) or the equivalent of 133 cases/100,000 population, the highest number in the Southeast Asia Region (44%). The top three countries are India (27%), China (9%) and Indonesia (8%). It is estimated that 3.5% of cases are multidrug-resistant tuberculosis (MDR-TB) and rifampicin-resistant tuberculosis (RR-TB) and 19% of these are cases previously treated with anti-tuberculosis drugs.[1]

Drug resistance research data indicate that an estimated 558,000 (483,000-639,000) MDR-TB/RR-TB, the highest number in China, India and the Russian Federation. There were 230,000 (140,000-310,000) people who died due to MDR-TB/RR-TB in 2017. At the end of 2017, it was reported from 127 countries that 8.5% of MDR-TB cases were accompanied by resistance to the fluoroquinolone class and the second-line injectable drug class (XDR-TB).[1]

Drug-resistant tuberculosis (DR-TB) has been treated well. However, it is still a global concern because, over the past few years, several studies have started to appear, showing that there has been a recurrence after DR-TB treatment. Reported recurrence rates varied across the globe from 0% after two years followed after recovery to 8.5% after eight years followed after recovery. DR-TB management currently available in the world requires too long a time (minimum 20 months), requires a large amount of money, both for the program and the patient. The program and the patient are factors that affect the success of DR-TB patient treatment.[2]

Worldwide DR-TB surveillance data also show unsatisfactory results in the long-term standard combination treatment success rate, which is around 50%. The management of DR-TB patients is a challenge for medical and public health professionals because drug options for treatment are limited and the threat of transmission will continue through contact with DR-TB patients.[2]

Disease recurrence is an important indicator of successful anti-tuberculosis treatment. Several studies have reported recurrencee rates after successful completion of DR-TB treatment. The study revealed that DR-TB recurrence could still occur, even in the condition of patients who received a combination of therapy individually. Recurrence rate was 0% after two years following in Nigeria, 3% after 4.8 years followed in Taiwan, 4.3% after 5.7 years in Hong Kong, 4.4% after two

years in South Korea, recurrence 5.2 % after two years followed in Peru and 8.5% after eight years in Estonia.[2–5] Examination of DR-TB patients who have recovered is considered very important to find the recurrence rate using sputum culture examinations every six months, done at least within the first two years after being declared cured.

Evaluation within 2 years after the patient is declared cured, meaning that patients who have recovered are re-evaluated for 2 years, are there any patients who have recurrence and relapsed within 2 years after recovering. Recurrence means that tuberculosis has recurred due to reactivation of the germs that have calmed down, meaning that the germs that have calmed down (dormant) are active again. While relapse means being infected again with a different germ or new germs entering. We were evaluating post-treatment drug-resistant TB (DR-TB) patients who came to control at months 6, 12, 18 and 24 to look for the recurrence and relapsed rate at the Persahabatan General Hospital Jakarta, Indonesia

METHOD

The research design was cross-sectional, conducted at the MDR pulmonary clinic of the Persahabatan General Hospital Jakarta from April 2017 - December 2017. The sample of the study was DR-TB patients who had been declared cured and had complete treatment in the last two years at the Persahabatan General Hospital Jakarta, who came to control at month 6,12,18 and 24. The sampling technique was *consecutive sampling*.

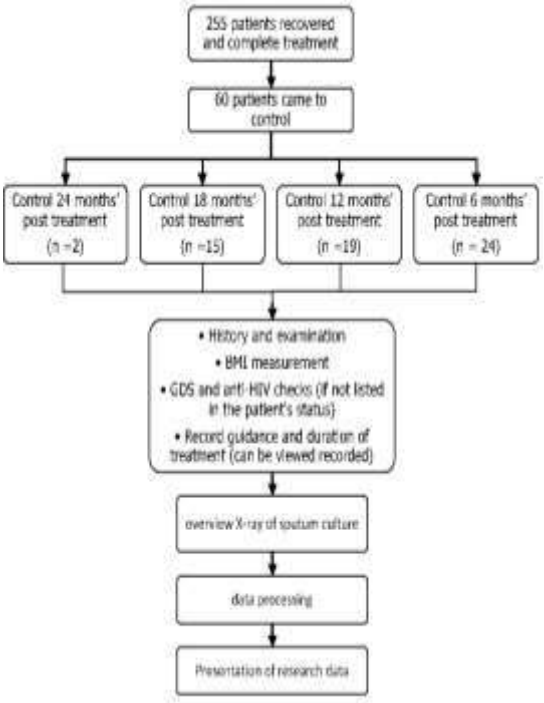

Figure 3.1. Research Flow

Acceptance criteria were patients are willing to participate in the study and sign informed consent and DR-TB patients who have been declared cured and patients who have completed treatment can undergo the research procedure. Rejection Criteria was DR-TB patients who had completed complete treatment and patients recovered but were unable to expel sputum, despite sputum induction.

This research procedure starts from DR-TB patients who have been declared cured and have complete treatment come to the Persahabatan Hospital pulmonary clinic, then screened whether they meet the criteria for acceptance and rejection. If the patient meets the admission criteria, the patient will be recorded as a participant and explained about the aims and procedures of the study. If the patient agreed, the patient signed informed consent to participate in the study.

Anamnesis was carried out regarding current complaints, measurements of body weight and height to calculate BMI. Doing a blood sugar check at a time and record the results of the anti-HIV examination listed in the patient's medical record. Records of the combination of drugs and duration of drug administration at the time of treatment are recorded. This data can also be seen in the patient's medical record.

The patient is asked to expel sputum, if the sputum cannot come out spontaneously then sputum induction is carried out, the sputum that has been accommodated is taken to the microbiology laboratory of the Friendship Hospital for culture and drug sensitivity testing using Ogawa 3% media and MGIT. Patients are asked to do a chest X-ray examination at the radiology department of Friendship Hospital. When there are results, the patient comes back with the results of the examination and is recorded as the results of the study.

RESULT

The research data collection was carried out at the MDR TB polyclinic Persahabatan General Hospital Jakarta from April to December 2017. The sample collection was carried out consecutively on DR-TB patients who had been declared cured and had complete treatment who came back for control at the Persahabatan Hospital in the first two years after recovering.

Sixty patients had been declared cured were included in this study. All patients who participated in the study met the inclusion criteria. The variables assessed in this study were characteristics which included age, sex, marital status, body mass index (BMI), final status of treatment, comorbid in the form of Diabetes Mellitus (DM) and Human Immunodeficiency Virus (HIV) infection, duration of DR-TB treatment, type of drug alloy given, lesion shape on chest X-ray at the time of control, clinical symptoms at control, type of resistance and sputum culture results taken at control.

Table 1. Profiles of DR-TB patients who recover/complete treatment who are controls over a specific period

Control Time	The number of patients come to control	The number of patients who recovered	Relative percentage of patients come to control
6th month	24	88	27.2 %
12th month	19	60	31.6 %
18th month	15	70	21.4 %
24th month	2	37	5.4 %
Total	60	255	23.5 %

The number of patients who have recovered and have complete treatment in the last two years is 255. It consists of 88 people who have recovered in the previous six months, 60 people who have recovered in the previous 12 months, 70 people who have recovered in the last 18 months, and 37 people who have recovered in the last 24 months.

Of these, we found 60 people who could be included in the study, consisting of 24 (27.2%) people who came to control at the sixth month, 19 (31.6%) people who came to control at month 12, 15 (21, 4%) people who came to control at month 18 and 2 (5.4%) who came to control at month 24. More details can be seen in Table 1. The number of patients who had been declared cured and had complete treatment was the same as the population, and the number of patients who came to control was the same as the number of samples.

The research subjects consisted of 31 males (51.7%) subjects and 29 (48.3%) female subjects with a mean age of 42.3 + 12.5 years. The research subjects were divided into three groups of age categories, namely 1 (1.7%) age <20 years, 41 (68.3%) subjects aged 20-50 years and 18 (30.0%) age> 50 years subject. Assessment of nutritional status with body mass index (BMI) obtained the nutritional status of underweight as much as 15 (25.0%), normal weight as much as 31 (51.7%), overweight as much as 11 (18.3%), and obesity as much as 3 (5.0%). There were 47 (78.3%) married patients, and 13 (21.7%) unmarried patients.

There were two patient statuses at the end of treatment, namely the recovered status of 58 (96.7%) subjects and the complete treatment status of 2 (3.3%) subjects. Recover in question is a patient who have completed treatment and ended up having a negative sputum test. If complete, the sputum was not checked when the treatment was finished at the end of the 6th month.

Table 2. Basic characteristics of subjects

Basic Characteristics	Number of Subjects (n=60)	
	n	%
Age		
<20 years old	1	1.7
20-50 years old	41	68.3
50 years old	18	30.0
Gender		
Male	31	51.7
Female	29	48.3
Nutritional Status		
Less weight	15	25.0
Normal weight	31	51.7
More weight	11	18.3
Obesity	3	5.0
Married Status		
Married	47	78.3
Unmarried	13	21.7
End of Treatment Status		
Recover	58	96.7
Complete Treatment	2	3.3
Diabetes mellitus		
Yes	16	26.7
No	44	73.3
HIV		
Yes	0	0.0
No	60	100.0
Treatment Regimen		
Conventional standard regimen	50	83.3
Individual regimen	10	16.7
Resistance type		
Rifampin resistant	15	25.0
Poli-resistant	1	1.7
MDR	36	60
Pre-XDR	7	11.7
XDR	1	1.7

There are 16 (26.7%) of patients with DM disease and 44 (73.3%) patients who did not have DM. All patients did not suffer from Human Immunodeficiency Virus (HIV) infection. Patients who received conventional standard anti-tuberculosis drug combination were 50 (83.3%) subjects, and 10 (16.7%) subjects received individual anti-tuberculosis drug combinations. Subjects consisted of several resistance patterns, namely rifampicin resistance (RR) 15 (25.0%), poly-resistance 1 (1.7%), multidrug-resistant (MDR) 36 (60%), pre-extensively drug-resistant (pre-XDR). 7 (11.7%) and extensively drug-resistant (XDR) 1 (1.7%) subjects. The description of patient characteristics in this study can be seen in Table 2.

An overview of body mass index (BMI) changes at the time of recovery compared to BMI at the time of control can be seen in Table 3. The mean BMI, when declared cured, was 20.75 + 4.06. Meanwhile, the average BMI at the time of control was 21.75 + 4.34. There was an increase in the mean BMI of patients after recovering from drug-resistant tuberculosis. By using the paired t-test, there was a significant difference between the mean BMI at recovery and the mean BMI at the arrival of control.

The median duration of treatment in months at the initial stage was 7.0 months, with a minimum duration of 5.7 months and a maximum of 10.4

months. The median duration of advanced treatment was 13.0, with a minimum duration of 10.8 months and a maximum of 20.1 months. The median total duration of treatment was 20.0 months, with a minimum duration of 18.9 months and a maximum duration of 29.2 months. An overview of the duration of treatment can be seen in Table 4.

Table 4. Overview of treatment duration

Duration of treatment	Median (min-max)
Early stage	7,0 (5,7 - 10,4)
Advanced stage	13,0 (10,8 - 20,1)
Total treatment	20,0 (18,9 – 29,2)

Table 3. An Overview of Changes in Body Mass Index

BMI	Average±SD	SD	95% CI	*P*
BMI healed	20,75±4,06	0,99±1,67	0,56-1,42	<0,001*
BMI control	21,75±4,34			

Note: *Paired *t* test

Table 5. Description of Clinical Symptoms Based on Time of Control, X-ray image on the arrival of the control

Variables	Time of Control			
	6 months (n=24)	12 months (n=19)	18 months (n=15)	24 months (n=2)
Clinical Symptoms				
There is no symptom	13 (54,1%)	16 (84,2%)	10 (66,7%)	2 (100%)
Cough	6 (25%)	1 (5,2%)	4 (26,6%)	0 (0%)
Cough + Tightness	3 (12,5%)	1 (5,2%)	1 (6,6%)	0 (0%)
Cough + chest pain	2 (8,4%)	1 (5,2%0	0 (0%)	0 (0%)
X-ray images				
Normal	0 (0%)	1 (5,2%)	2 (13,3%)	0 (0%)
Fibroin filtrates+calcification	12 (50%)	9 (47,3%)	8 (53%)	1 (50%)
Bronchiectasis	3 (12,5%)	3 (15,7%)	0 (0%)	0 (0%)
Atelectasis	4 (16,6%)	0 (0%)	1 (6,7%)	1 (50%)
Cavity	0 (0%)	2 (10,5%)	1 (6,7%)	0 (0%)
Bulla	2 (8,3%)	1 (5,2%)	1 (6,7%)	0 (0%)
Destroyed Lung	2 (8,3%)	3 (15,7%)	2 (13,3%)	0 (0%)
Nodules	1 (4,1%)	0 (0%)	0 (0%)	0 (0%)
X-ray category overview				
Normal	0 (0%)	1 (5,6%)	2 (13,3%)	0 (0%)
Minimal Lesions	3 (12,5%)	5 (15,8%)	1 (6,7%)	1 (50%)
Extensive Lesions	21 (87,5%)	15 (78,8%)	12 (80%)	1 (50%)
Culture Results				
Positive	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Negative	24 (100%)	19 (100%)	15 (100%)	2 (100%)

Patients who came to control in the sixth month mostly had no symptoms, namely 13 (54.3%), 6 (25%) cough symptoms, 3 (12.5%) coughs accompanied by chest pain, and 2 (8), 3%). In the group of patients who came to control at the twelfth month, 16 (84.2%) had no symptoms, 1 (5.2%) cough, 1 (5.2%) cough accompanied by pain, and 1 (5.2%) cough accompanied by pain. The chest is 1 (5.2%). In the group of patients who came to control in the eighteenth month, there were 10 (66.7%) patients who did not complain of symptoms, 4 (26.6%) coughed, 1 (6.6%) cough with shortness. Patients who came to control at the twenty-fourth month, as much as 2 (100%) had no clinical symptoms. The clinical symptoms complained of by patients when they came to control can be seen in Table 5.

In the group of patients who came to control at the sixth month, there was no normal chest X-ray, 12 (50%) fibroinfiltrates and classification, 3 (12.5%) bronchiectasis, 4 (16.7%) atelectasis, 0 cavities (0 %), bullae as much as 2 (8.3%), lung yield as much as 2 (8.3%) and nodule appearance as much as 1 (4.1%). In the group of patients who came to control at the twelfth month, there was a normal chest X-ray image of 1 (5.2%), 9 (47.3%) fibroinfiltrates and calcifications, 3 (15.7%) bronchiectasis, 0 (0) atelectasis. %), cavities as much as 2 (10.5%), bulla as much as 1 (5.2%), lung yield as much as 3 (15.7%), and nodule appearance 0 (0%).

In the group of patients who came to control at the eighteenth month, 2 (13.3%) normal chest radiographs, 8 (53.3%) fibroinfiltrates and calcifications, 0 (0%) bronchiectasis, 1 (6,7%) atelectasis %), cavities, bulla as much as 1 (6.7%), lung yield as much as 2 (13.3%) and nodule appearance 0 (0%). In the group of patients who came to control at the twenty-fourth month, there was a normal chest X-ray image of 0 (0%), fibroinfiltrates and calcifications as much as 1 (50%), bronchiectasis 0 (0%), atelectasis as much as 1 (50%), cavity 0 (0%), bulla 0 (0%), lung yield 0 (0%) and nodule appearance 0 (0%). The description X-ray images are summarized in Table 5.

The description X-ray images we categorize into standard description X-ray images, minimal lesions, and extensive lesions, can be seen in Table 4.7. Chest X-ray image at the time of sixth-month control was normal picture 0 (0%), minimal lesions were 3 (12.5%), extensive lesions were 21 (87.5%). Chest X-ray image at the time of arrival at the twelfth month of control was normal, as much as 1 (5.6%),

minimum lesions were 3 (15.8%), extensive lesions were 15 (78.8%).

The description X-ray at the eighteenth-month control time was normal, as much as 2 (13.3%). And the minimal lesions as much as 1 (6.7%) and extensive lesions as much as 12 (80%). The description X-ray image at the arrival time at the twenty-fourth-month control was no normal photo image, the minimum lesion picture was 1 (50%), and the extensive lesion picture was 1 (50%).

An overview of the culture results of *Mycobacterium tuberculosis* can be seen in table 4.8. The *M.tb* culture results in the sixth month of control were positive 0 (0%), 24 negative results (100%). The result of *M.tb* culture when the control came in the twelfth month was positive 0 (0%), negative results 19 (100%), the result of *M.tb* culture when the control came in the eighteenth month was positive 0 (0%), negative 15 (100%), the result of *M.tb* culture when the control came in the twenty-fourth month was positive 0 (0%), negative 2 (100%).

DISCUSSION

Based on the guidelines for the administration of drug-resistant tuberculosis known as Programmatic Management of Drug-Resistant Tuberculosis (PMDT) that patients who have undergone treatment of drug-resistant tuberculosis should remain evaluated at least 2 years after completing treatment. Evaluation is carried out every six months by conducting an examination of sputum breeding in patients who have been declared cured or complete treatment. This is important for early detection of recurrence in patients so that it can be given quick and precise treatment. Previously, the patients have been educated about the importance of regaining control after recovery.[6]

Researchers took data on when patients came to control in the sixth, twelfth, eighteenth and twenty-fourth months. All patients who control come with their awareness following a control schedule that has been determined by the officer. From the data, it obtained by four groups of patients based on the time the patient came to control. The largest group of patients were patients who came under control in the sixth month, and the least was the group of patients who were in control in the twenty-fourth month.

This study is a cross-sectional study so that the patients studied are different people in each group based on the control time. This data showed that the longer the distance between time healed and control time, the lower percentage of patients who came to

control. Control declared cured, and complete treatment aims to track recurrence so that when the patients found a recurrenced, it can be treated immediately.

In this study, the most age group was the productive age group of 20-50 years old, which is 41 (68%) Patients. This finding is similar to Librianty N et al. 's research that the age of drug-resistant TB patients in Persahabatan Hospital is 18-40 years old by 58.5% and age 41-60 years old as much as 36.7%. The findings are similar to the TB-RO recurrence study conducted by Chen MY et al. in Taiwan. They found that most subjects in the study were aged 35-60 years, which was 55.8%. Lee J et al. research in Korea found the study subjects' median age was 33.0 (26-50) years. This finding corresponds to the literature that the most suffering from tuberculosis disease is the productive age group.[2,7,8]

This study found that men were more found to be 31 (51.7%) Patients. These findings are similar to research conducted by Librianty N et al., they found that the most drug-resistant TB sufferers were men by 56.9%. The same things were also found in the research conducted by Chen MY et al., finding that the number of men was 77.2%, and research conducted by Lee J et al. found that male subjects were 56.7%. These findings correspond to the results of previous studies that number is more men than women. This is because men are more active outdoors than women, so men are more likely to get infections from outdoor environments. Besides, men also smoke more than women. Smoking is one of the factors that can cause tuberculosis infection.[2,7,8]

In this study, the married status was obtained for 47 (78.3%) people. A spouse or husband can become supervisors for taking medication in accordance with the government policy that a person who is currently taking anti-tuberculosis drugs must be supervised by the Drug Administration or Pengawas Minum Obat (PMO). In drug-resistant TB treatment, the PMO is a health worker, but the success of treatment cannot be separated from the role of family members, who will always remind patients to come to a health facility to get treatment according to the specified time.

In this study found 58 (96.7%) patients have recovered, then patients and complete treatment of 2 (3.3%) patients, namely one patient who came to control in his sixth month and one patient who came to control in the twelfth month. These two patients did not issue phlegm at the end of the treatment because there was no

phlegm production even though there had been sputum induction. Patients with complete treatment status are more at risk of recurrence than patients who are cured because, in those patients, it cannot be proven that the results of the sputum examination are negative at the end of treatment because there is no production of sputum.[2,8,9]

In this study, the relationship between the final status of treatment and recurrence could not be analyzed because none of the patients recurrenceed. A study conducted by Lee J et al. in Seoul found a recurrence rate of 4.4%, with four recurrenceed patients among the 90 patients studied. All patients who recurrencee are full of treating patients. The same research conducted by Chen MY et al. in Taiwan found that more patients with complete treatment were 7% more likely to experience recurrence than only 3% of patients who had a recurrence. The same was also found in research conducted by Cox H et al. in Uzbekistan that recurrencees were more common in patients with complete treatment status of 47% compared to patients with cured status of 31% with P=0.02.[2,8,9]

In this study, there were 16 (26.7%) patients who are suffering from DM but cannot be analyzed because no patients that recurrencee. Diabetes Mellitus is a predictor factor for recurrence if not appropriately treated. Patients suffering from DM should have a blood sugar test and HbA1c every time they come under control to ensure the disease is well controlled so that recurrence can be avoided. In this study, blood sugar and HbA1c were not performed due to researchers' limitations and were not included in the research procedure. A study conducted by Chen MY et al. in Taiwan found that TB-RO patients suffering from DM had a higher recurrence rate of 5% compared to TB-RO patients who did not suffer from DM who had a recurrence rate of only 3%. Research conducted by Franke MF found that TB-RO patients suffering from DM were also an influential factor in the recurrence of the disease. According to research by Fisher-Hock, SP et al. found that TB-RO patients who had DM disease had low output. The results of some of these studies give an idea that DM can be an influential factor in TB-RO recurrence, but if DM can be adequately handled, then recurrence can be avoided.[2,10,11]

HIV infection increases the risk of tuberculosis recurrence. Based on e-TB manager data from 2013 to 2015, the number of people with HIV is estimated at 3.5%. Of these, patients who

recovered 1.3%, negligent patients had 1.5% treatment and patients who died 0.6%. In this study, there were no patients infected with HIV because of the small number, and this may be one of the factors that did not occur recurrence in the patients studied. Chen et al. concluded from the results of his study that the recurrence of common drug-resistant tuberculosis was 3.4% due to one of the factors because people with HIV lacked only 2% of all the study subjects. Gelmanova et al. concluded that the low recurrence rate of TB-MDR due to its study subjects was 99.7% HIV negative. According to research conducted by Marin et al. that tuberculosis patients infected with HIV have a 3.3 times risk of recurrence compared to tuberculosis patients without HIV infection.[2,4,12]

In this study, there were 45 (75 %) subjects who have normal nutritional status and more nutrition, 15 (25 %), which has malnutrition status. One of the factors that play a role in the recurrence is of low nutritional status. In this study, there was no recurrence because most subjects had good nutritional status. But there are 15 (25%) subjects that have malnutrition status but do not occur recurrence. It is because, despite the lack of nutritional status, the patient undergoes an improvement in nutritional status that can be assessed from a significant increase in average body mass index (BMI) after the patient recovers $P<0.001$. There is no recurrence in the malnourished subject group, and it can be explained that improving nutritional status can prevent a recurrence. According to Marin et al., the result showed that malnutrition status is less associated with recurrence risk. It fits the theory that an increase in body mass index can improve the body's ability to fight infection.[12,13]

In this study, the average duration of early-stage treatment is 7 months 24 days + 1 month 14 days, the average duration of advanced treatment is 14 months 1 day + 2 months 29 days. The average total duration of treatment is 21 months, 25 days + 1 month, 7 days. This finding is following TB-RO treatment guidelines in Indonesia, which is at the initial stage at least 6 months or 4 months after the conversion of breeds, and the total duration of treatment is at least 18 months. There are 2 patients who underwent the initial treatment duration less than 6 months. This is because the patient has been converted in the first month, so the initial stage is only 5 months, which is 1 month plus 4 months, then continued to the advanced stage.[10]

All patients in this study underwent treatment for more than 18 months, which led to no recurrence because all patients had been given the right combination of medications and treatment length following TB-RO control guidelines. According to research conducted by Franke et al. in Peru states that patients receiving TB MDR treatment with a combination of aggressive treatment that is a treatment given at least 18 months after conversion can reduce the recurrence rate. In this study, some patients received treatment less than 18 months after conversion, but there was no recurrence, this was due to the combination of drugs given according to the results of the drug sensitivity test, and the alloy was significant enough to kill germs.[10]

RR patients and MDR TB patients get a mixture of conventional standard drugs. Polyresistic TB, pre-XDR TB, XDR TB, and 1 MDR TB patient who experienced intolerance to conventional standard drug alloys got individual drug alloys. Pre-XDR TB and TB XDR are possible factors that allow recurrence due to the lack of a drug alloy sensitive to germs M. Tuberculosis that causes pre-XDR TB and TB XDR. But in this study, there was no recurrence despite the cases of pre-XDR TB and TB XDR, it because the patient had been treated with an individual alloy that matched the results of the drug sensitivity test. But these patients are still at risk for recurrence, therefore having to keep monitoring once every six months in the first two years after being declared cured.[2,14]

In contrast to the research conducted by Chen, MY et al. revealed that among 15 TB XDR patients, there was 1 patient (7 %) recurrence. Among 43 pre-XDR TB patients, there was 3 patients (7%) recurrence compared to MDR recurrence patients only occurred in 4 patients (3 %) among the 157 patients. Research conducted by Blondal et al. in Estonia states that drug-resistant TB recurrence is associated with resistance to second-line injectable drugs (HR 2.27, 95% CI 1.16-5.06, p = 0.04) and resistance to some kinds of drugs (HR 2.16, 95% CI 1.11-1.64, p = 0.016).[2,14]

Most of the patients in each group did not complain of clinical symptoms. Among the 60 patients, only 19 (31.7) patients complained of respiratory symptoms after being declared cured. Symptoms that are still complained about are coughing, coughing accompanied by tightness, and cough accompanied by chest pain, especially new patients who just completed the treatment that came under control in the 6th month. Compared to the group

of patients who came to control in the 6th month with the group of patients who came in the 12th month, more symptoms were found in the group of patients in control in the 6th month; most symptoms were coughing.

This finding contrasts with research conducted by Singla N et al. in New Delhi found that among the 51 patients studied, 40 (78%) patients are still complaining of residual symptoms. The most common remaining symptoms were tightness of 53%, phlegm cough 43%, cough accompanied by tightness 31%, and who did not complain of symptoms as much as 22%. Meanwhile, Singla R et al. in New Delhi found that among 46 patients, 44 (95.7%) still have the most symptoms, and symptoms are tightness as much as 40 (87%).[15,16]

In this study, most of the thorax photos in the form of images of fibroinfiltrates and calcification. It is appropriate in the literature that the picture of fibrosis and calcification is a sign of inactive tuberculosis. There are 3 patients (5 %) with a thin-walled cavitation picture in the thorax photo, 2 were obtained in the group of patients who came under control in the 12th month, and 1 was obtained in the group patients who came to control in the 18th month. Chest X-ray image in the form of a cavity is a risk factor for recurrence of drug-resistant TB because it is associated with poor drug penetration into the cavity and the large number of germs in the cavity so that even though aggressive drugs have been given, the results achieved are not optimal. But in this study the relationship between cavity and recurrence could not be analyzed because none of the patients had recurrencees.

A study conducted by Chen MY et al. in Taiwan expressed the idea that the thorax photo's cavities are an essential factor in drug resistance. In the study revealed that of the 124 patients who found cavities in the thoracic, there are 8 (7%) patients who experienced recurrence, compared to 171 patients who did not have a picture of the cavities, there are only 2 (1%) patients experienced recurrence with a P=0,03. Chen MY's findings are similar to the results of research conducted by Marin et al., they state that cavitation in the photos of the thorax is closely related to the risk of tuberculosis recurrence.[2,17]

There are two thorax photos with an infiltrated image, obtained in the group of patients who came to control in the 6th month. The infiltrate image is a sign of active infection, but this picture is still obtained in patients who have been declared cured. A photo of

fibroinfiltrates and pulmonary damage found by patients who came under control in the 6th, 12th, and 18th months, this image shows a wide pulmonary abnormality. There is one picture of nodules found in the month of the patient that comes to control in the 6th month, a picture of nodules rarely found in pulmonary patients. This patient needs to be explained that the nodules seen in the thorax photo should be further examined, such as CT-scans of the thorax and Bronchoscopy, to find out the nodules the possibility of a tumor or abnormality due to tuberculosis infection.

The findings are similar to research conducted by Singla N et al. in New Delhi, and they found that among 45 patients, the normal thorax photo picture was only 1 (2%), a minimum lesion of 16 (36%) and 28 (46.7%). A cavities picture was found in 24 (53%). While according to Singla R et al. research reporting that 46 patients were studied, all patients had a picture of bilateral radiology abnormalities, 82.6% had a comprehensive view of pulmonary abnormalities, 17% had a broad pulmonary view, and no minimal lesion pulmonary abnormalities were found. Multiple cavities reported as many as 24 (52.2%).[15,16]

The standard in the diagnosis of tuberculosis is the culture of M. tuberculosis. There are two ways that can be used to breed *Mycobacterium tuberculosis*, namely using solid media for Lowenstein-Jensen (LJ) and Liquid Media Mycobacterium Growth Indicator Tube (MGIT). Conventionally bacterial cultures are carried out in Lowenstein-Jensen (LJ) media.

The advantage of this conventional culture is the low cost with a simple procedure. At the same time, the disadvantage is that it takes a long time. Culture using the LJ medium takes about 20-56 days for diagnosis and 4-6 weeks after culture for drug sensitivity tests. It has the effect of delaying therapy for patients who are positive for bacterial culture. BACTEC MGIT is a growing medium for *Mycobacterium sp* bacteria.

The advantage of MGIT is that the culture time is relatively shorter than the culture in LJ media. Based on Hanan et al. research in 2008, the average growth of Mycobacterium tuberculosis in BACTEC MGIT 960 was 4.6 days, while in LJ, it took 37 days. Besides, Setiarsih et al. research in 2010 stated the average time it takes to detect Mycobacterium tuberculosis in medium MGIT 960 is 16 days, while it takes an average of 32 days on medium LJ.

The disadvantage of BACTEC MGIT is the number of contaminant

bacteria that can grow because it is a liquid medium. Some studies say higher levels of contamination occur in liquid media than solid media. Contamination rates in Mycobacterium tuberculosis cultures were 8.5% for BACTEC MGIT and 3% for LJ.

This study has many limitations, this study is not a cohort study, so it does not follow the patients who come to control every 6 months. The distribution of evaluated patients is not the same between the four groups, especially in the group of patients who came to control in the 24th month; the number is minimal compared to the number in the group that came control in the 6th month. The patients evaluated are patients who come passively, i.e., These patients come because of their awareness for control. There is no active search of the subject, and the thorax photo does not compare to the previous photo.

CONCLUSION

The number of patients who come to control is getting less between recovering and the control schedule. In this study found that out of 60 patients evaluated, there was no recurrence. Factors that affect recurrence cannot be analyzed because, in the study, no patients recurrenceed.

Researcher suggest to evaluation at month 18 and month 24 needs to be improved by doing home visits all patients who have been declared cured to determine the condition of patients who have completed treatment; it is necessary to evaluate all patients who have to declare cured and complete treatment once every six months, at least the first 2 years after recovery, which is carried out actively by the program's officers and managers and in cooperation with health centers and health services; it is necessary to conduct cohort research on patients who have been declared cured and complete treatment with a longer research duration; It is necessary to provide a separate room between the patient who has been declared cured and the patient whose complete treatment comes control, and the patient is still undergoing treatment; and patient data recording should be filled completely in the patient status and in the program management computer.

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ORIGINAL ARTICLE

Accuracy of Circulating Tumor DNA (ctDNA) in EGFR Mutation Detection Among Lung Adenocarcinoma in M Djamil Hospital, Padang

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ABSTRACT

Background: ctDNA is an alternative test for detecting mutation of EGFR in lung cancer type adenocarcinoma if the tissue speciment can not be carried out. Sensitivity, specificity and accuration of ctDNA test is stil varied. This study is aimed to acknowledge sensitivity, specificity and accuration of ctDNA in detecting EGFR mutation in patient with lung cancer type adenocarcinoma in M Djamil Hospital.

Methods: Design this study a diagnostik test comparing ctDNA to tissue speciment in detection EGFR mutation of 42 patients with lung cancer type adenocarcinoma in M Djamil Hospital. Sample was selected through consecutive technique.

Results: Incidence of EGFR mutation in patients with lung cancer type adenocarcinoma from tissue speciment was higher than ctDNA ((42,9% vs 28,6%; p=0,031). There was significant diffierence of EGFR mutation detection between sex, smoking status, and TNM staging based on tissue/cytology examination and ctDNA (p=0,031). EGFR mutation in sitologic test and ctDNA was more likely detected in male patient (66.7% and 58.3%), ex-smoker (50% and 41.7%) and stage IV (88.9% and 91.7%). The results of sensitivity, specificity positive prediction value (PPV) and Negative prediction value (NPV) in ctDNA test to detect EGFR mutation were 66,7%, 100%, 100% dan 80% according to sitology test as gold standard. Furthermore, the ctDNA accuration was measured according to AUC score 0.833 (SE 0,072, CI 95%, 0,693-0,974, p=0.0001).

Conclusion: ctDNA test have a good accuration with sensitiviy 66.7% and specificity 100% in detecting EGFR mutation in patients with lung cancer type adenocarcinoma.

Keywords: EGFR, lung cancer, adenocarcinoma, ctDNA

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INTRODUCTION

Adenocarcinoma is the most common non-small cell carcinoma (KPKBSK) type lung cancer in Indonesia.[1] The treatment of adenocarcinoma lung cancer has undergone many developments including using targeted therapy. Tyrosine kinase inhibitors (TKI) are one of the target therapies given to KPKBSK with epidermal growth factor receptor (EGFR) mutations.[2]

EGFR mutation examination specimens are derived from tissue specimens or cytology, provided that the number of cells is sufficient. A common obstacle is the small number of cells in the specimen and the difficulty of retrieving tissue specimens.[2] Therefore, an alternative examination is required that can detect EGFR mutations with lower invasive rates and good accuracy.[3]

EGFR mutations were first reported in 2004 and EGFR mutations in tyrosine kinase in pulmonary adenocarcinoma patients have been the main focus of research in understanding pathogenesis and current treatment.[4] EGFR mutation screening is a requirement to obtain TKI as a targeted therapy in pulmonary adenocarcinoma.[5]

Multisenter research in Indonesia by Syahruddin et al against 1874 newly diagnosed lung cancer shows the frequency of EGFR mutations 44.5%. The most common obstacle found in the examination of EGFR mutations from this study is the number of tumor cells obtained from too few cytological specimens (<100 cells). The problem is one of the causes of failure in the examination of EGFR mutations which is as much as 95 (5.1%) Specimens.[6]

One alternative EGFR mutation examination other than cytological specimens or tumor tissue is circulating tumor DNA (ctDNA) test using blood specimens.[3] In research conducted by Bettegowda et al., found that patients with pancreatic, ovarian, colorectal, urinary vesical, gastroesophageal, breast, melanoma, hepatovascular and head and neck cancers who have metastatic, ctDNA examination can detect EGFR mutations more than 75% pasien.[7]

In reck et al., research, only 9% of lung cancer patients with EGFR mutation positive from ctDNA screening in several European countries and Japan.[7] In contrast to zaini et al., research at RSUP Persahabatan Jakarta, 41.8% of lung cancer patients with EGFR mutation detected from ctDNA examination. In the study also found that sensitivity was 30-40% and specificity 83%-96% in ctDNA examination in detecting EGFR

mutations of patients before getting treatment.[8]

METHOD

This research is a diagnostic test study comparing ctDNA examination with tissue examination/cytology in 42 KPKBSK patients of adenocarcinoma type in RSUP. DR. M. Djamil Padang from March 2019-February 2020.

Samples are taken on a nonprobable way with consecutive techniques. Inclusion criteria are Patients with previous chemotherapy-naive (never had chemotherapy before), have no other inorgan malignancy, willing to participate in research and sign informed concerns. While the exclusion criteria is the number of tumor cells in tissue specimens/cytology less than 100 cells.

The research sample was then examined for EGFR mutations through tissue/cytology and ctDNA plasma in a patient at the same time. Examination of EGFR mutations through tissue /cytology is carried out by sending slides of cytological anatomical pathology or pulmonary adenocarcinoma tissue to CITO clinical laboratory Yogyakarta. CtDNA examination is carried out through a 5 ml venous blood specimen taken by prodia jakarta clinical laboratory staff.

The research has been approved by the ethics committee of RSUP Dr. M. Djamil Padang. Statistical analysis used is diagnostic test (sensitivity, specificity, positive prediction value (NPP), negative prediction value (NPN)) using test performance table 2x2. In this study, EGFR mutation examination of tissue/cytology as diagnostic reference /gold standart and EGFR mutation examination of ctDNA as diagnostic index. To assess the accuracy of ctDNA checks used ROC curve analysis (receiver operating characteristic) with output of Area Under Curve (AUC).

RESULT

This research is a diagnostic test study that includes patients as a sample of 42 people who are treated to poly pulmonary or treated in the pulmonary ward of RSUP Dr. M. Djamil Padang. The results showed that the majority of patients were male (81.0%). The average age of patients in the study was 58.9±10.07 years, with the youngest age being 34 years old and oldest 79 years. More than half (54.8%) patients are former smokers and have TNM staging IV (73.8%). A total of 52.4% of patient specimen retrievals were carried out by transthoracic needle aspiration (TTNA) method, as seen in Table 1.

The incidence rate of EGFR mutations in KPKBSK patients of adenocarcinoma was assessed based on more tissue specimens/cytology compared to ctDNA (42.9% vs. 28.6%; P=0.031). The most mutations were found in exon 19 insertions/deliesthesia, both in tissue specimens/cytology (77.8%) ctDNA (66.7%) (Table 2).

The results of the analysis showed that there were differences in detection of EGFR mutations in gender, smoking status, and TNM staging based on tissue/cytology and ctDNA (P=0.031) (Table 3). In the results of the study also found that EGFR mutations were widely detected in former smokers at tissue/cytological examination (50.0%). While in ctDNA examination, EGFR mutations were widely detected in former smokers (41.7%) and non-smoking (41.7%) (Table 3). Positive EGFR mutation detection was found in stage IV patients from both tissue/cytological examinations (88.9%) ctDNA (91.7%).

Table 1. Characteristics of KPKBSK patients with adenocarcinoma at RSUP DR. M. Djamil Padang

Characteristics	**n**	**(%)**
Gender		
Male	34	81,0
Female	8	19,0
Age (Mean±SD)	58,90±10,07	
Smoking Status		
Smokers	11	26,2
Ex-smokers	23	54,8
No smokers	8	19,0
TNM staging		
I + II	0	0,0
IIIa	5	11,9
IIIb	6	14,3
IV	31	73,8
Specimen Retrieval Method		
Cytological sputum	1	2,4
Pleural fluid cytology	4	9,5
Fine needle aspiration biopsy (BJAH)	2	4,8
Transthoracic needle aspiration (TTNA)	22	52,4
Core Biopsy	4	9,5
Rinse the bronchial	3	7,1
Bronchial sikatan	5	11,9
Bronchial forcep biopsy	1	2,4

Table 2. Incidence of EGFR mutation of KBKBSK patients of adenocarcinoma type in RSUP. Dr. M. Djamil Padang

Mutasi EGFR	**Tissue specimens/cytology**	**ctDNA**	**P**
Positive	18 (42,9%)	12 (28,6%)	0,031
Common mutation			
Exon 19 insertion/deletion	14 (77,8%)	8 (66,7%)	
Exon 21 (L858R)	2 (11,2%)	3 (25,0%)	
Uncommon mutation			
Exon 18 (G719X)	0 (0,0%)	0 (0,0%)	
Exon 20 (T790M)	0 (0,0%)	0 (0,0%)	
Mix mutation			
Exon 21, Exon 20 (T790M)	2 (11,2%)	1 (8,3%)	
Negative (wild type)	24 (57,1%)	30 (71,4%)	

Table 3. Differences in positiveness of EGFR mutations based on gender, smoking status, and TNM staging.

Characteristic	**EGFR mutation detection**		**P**
	Tissue/cytology (n=18)	**ctDNA (n=12)**	
Gender			
Male	12 (66,7%)	7 (58,3%)	0,031
Female	6 (33,3%)	5 (41,7%)	
Smoking Status			
Smokers	3 (16,7%)	2 (16,7%)	
Ex-smokers	9 (50,0%)	5 (41,7%)	0,031
No smokers	6 (33,3%)	5 (41,7%)	
TNM staging			
I + II	0 (0,0%)	0 (0,0%)	
IIIa	2 (11,1%)	1 (8,3%)	0,031
IIIb	0 (0,0%)	0 (0,0%)	
IV	16 (88,9%)	11 (91,7%)	

The results showed that the examination had a sensitivity of 66.7%, meaning that ctDNA's ability to detect positive EGFR mutations was 66.7%. While the result of specificity is 100%, it means that ctDNA's ability to detect negative EGFR mutations is 100% (Table 4). The proportion of patients with positive ctDNA results (positive prediction value/NPP) is 100% and negative prediction value (NPN) is 80%.

ROC curve analysis shows that the area value below the AUC curve is 0.833, standart error (SE) 0.072, confidence interval 95% (CI 95%) 0.693-0.974 with P=0.0001. This value can be interpreted as ctDNA's ability to tissue/cytology to accurately detect

EGFR mutations classifying positive and negative EGFR mutation detection as 0.833. Because the value is large enough can be interpreted that the level of accuracy of the examination is good. Statistical test results also show that the P<0.05, it can be concluded that ctDNA examination is proven to have the ability to distinguish the detection of positive and negative EGFR mutations (Figure 1).

Table 4. ctDNA Diagnostic Test Results on Tissue/Cytology in Detecting EGFR Mutations

ctDNA	Tissue/cytology		Total
	Positive	Negative	
Positive	12 (66,7%)	0 (0%)	12 (28,6%)
Negative	6 (33,3%)	24 (100%)	30 (71,4%)
Total	18 (100%)	24 (100%)	42 (100%)
Sensitivity=66,7%		NPP=100%	
Spesificity=100%		NPN=80%	

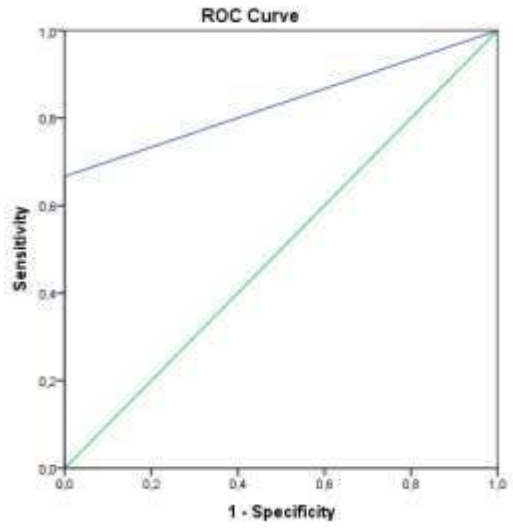

Figure 1. Accuracy of ctDNA against tissue / cytology in detecting EGFR mutations

DISCUSSION

This study found that the mean age was 58.90±10.07 and was common in men (81.0%). %). Many studies have found that people with lung cancer are more than 40 years old.[9] Research by Siegel et al. Found that the average age of lung cancer patients in the United States is 55-74 years.[10] The risk of lung cancer increases with age. Previous cell damage can take years to develop into cancer.[11]

The older you get, the longer you are likely to be exposed to various risk factors for lung cancer, followed by a decrease in the ability to repair cells.[11] Male gender is also a risk factor for lung cancer.[12] Based on data from the American Cancer Society, the number of lung cancer cases continued to increase in 2018, especially in men, as many as 121,680 instances from 234,030 total lung cancer cases.[9]

This study also found that lung cancer patients were still smokers (26.2%) and former smokers 54.8%, all of whom were male. Secondhand smoke exposure is one of the main risk factors for lung cancer in men and women.[13] This data is also supported by other studies that found that nearly 90% of lung cancer incidence was caused by cigarette smoke exposure.[9] The risk of smokers who have lung cancer is 10-30 times higher than

nonsmokers.[14] The incidence of lung cancer in smokers is influenced by age at initiation of smoking, the number of cigarettes smoked per day, length of the smoking habit, and smoking cessation duration.

The most common stage found in this study was stage IV (73.8%). Research conducted by Wang et al. in East China in 2011-2015 found that the most stage lung cancer found was stage IV (59.4%), and 62.2% were adenocarcinoma types. In the research conducted by Zaini et al. At Persahabatan Hospital, Jakarta, 42.45% of patients with stage IIIB and IV adenocarcinoma lung cancer were reported. Delay in diagnosis is one of the most common factors causing the high incidence of lung cancer patients with stage III and IV when the diagnosis is made.[15]

In this study, obtaining TTNA (52.4%) took the most specimens to get the most adenocarcinoma cell types with a cell count> 100. TTNA is a method of collecting cytological specimens that is most commonly used in lung cancer patients.[16] In general, Indonesia is the country with the highest detection of EGFR mutations through the cytological specimen method (98.0%).[17] One of cytology specimens' problems in detecting EGFR mutations is the insufficient number of tumor cells (<100 cells).[6]

The EGFR mutations detected from tissue/cytology, and ctDNA examinations were 42.9% and 28.6%, with the most exon 19 insertions/cell lesions mutations found (66.7%). This study's results were higher compared to studies conducted by Reck et al. In patients in Europe and Japan, where the incidence of EGFR mutations in adenocarcinoma from tissue/cytology and ctDNA was 20% and 11%.[7]

Based on Indonesia's multicenter research, the EGFR mutations detected were no different from this study, namely as much as 44.5%.[6] However, in Zaini et al.'s study at the Friendship Hospital, 62.7% and 41.8% of EGFR mutations from tissue/cytology and ctDNA examinations were obtained, which were higher than this study.[8]

Besides, many exon 19 mutations were found in previous studies, namely as much as 85% to 90%, so that mutations in exon 19 and L858R on exon 21 are called classic mutations or common mutations of EGFR in adenocarcinoma lung cancer.[5] Research by Zaini et al. at the Friendship Hospital in 2016 found EGFR mutations on exon 19 and L858R on exon 21, getting 15.45% and 21.8% (tissue/cytology) and 5.45% and 13.6% (ctDNA).[8] EGFR mutations in lung cancer were found on average in

women, Asian races, and non-smoking with adenocarcinoma type (60%).[18] In our study, men had a higher detection of EGFR mutations through tissue/ cytology examination (66.7%) and ctDNA (58.3%). The level of EGFR mutation positivity in tissue/cytology and ctDNA examinations also differed by sex. Li et al.'s study found the detection of EGFR mutations associated with patient sex and smoking history.[19]

This study also found that EGFR mutations were mostly detected in former smokers through tissue/cytology (50.0%), and through ctDNA examination, they were found in former smokers (41.7%) and non-smokers (41.7%). The results of our study analysis also found that there was a difference between the detection of EGFR mutations on tissue/cytology and ctDNA based on smoking status. Research by Tseng et al. (2017) reported that the average EGFR mutation in smokers and non-smokers was 41.9% and 70.0%. In that study, age, gender, smoking status were also predictors of the low mean level of EGFR mutation positivity. Smoking is known to be a negative predictor of the detection of EGFR mutations.[19,20]

A meta-analysis study by Ren et al. confirmed that non-smokers were significantly associated with high rates of detection of EGFR mutations.[20] Pham et al.'s study assessed smoking degrees by the pack and smoke-free years on the prevalence of detection of EGFR mutations. The study found that the EGFR mutation was not much different between non-smokers and patients who had smoked <15 pack-years or the length of time they quit smoking. Tseng's study also found that smoking at a young age had a low EGFR mutation.[19,20]

The study by Wiencke et al. Found that the level of abduct DNA in the carcinogenesis process was inversely related to the age at initiation of smoking among former smokers.[19] This suggests that young smokers are more susceptible to DNA damage and persistent genetic changes than patients who start smoking at an older age.[20] The high EGFR mutations in former smokers from the current study were likely influenced by the number of cigarettes consumed, age at initiation, and length of time to quit smoking.

This study showed the highest EGFR mutations in stage IV patients, both from tissue/cytology examination (88.9%) and ctDNA (91.7%). There are also differences in the detection of EGFR mutations in TNM staging characteristics based on tissue/cytology and ctDNA examinations. The results of Oh et al.'s study in Korea (2019) found that

positive EGFR mutations were also the highest in stage IV, both from tissue/cytology (53.4%) and ctDNA (32.0%). The high EGFR mutation in stage IV lung cancer patients is probably due to the tumor's spread into the circulation during the metastasis process.[21] In daily practice, differences in metastatic stage and status can significantly influence the detection of EGFR mutations in plasma, considering that ctDNA release is influenced by tumor size and metastatic processes.[22]

Identifying EGFR mutations in the adenocarcinoma type of KPKBSK is an essential guide for clinicians as a basis for providing targeted therapy. Several previous studies have suggested ctDNA plasma examination as an alternative to detect EGFR mutations in lung cancer.[23] Our research got a moderate sensitivity of 66.7% but with a specificity of 100%, NPP 100%, and NPN 80%. The ASSESS study on 1162 patients found that plasma ctDNA was a good test for detecting EGFR mutations in lung cancer with a 46% sensitivity, 97% specificity, NPP of 78%, and NPN of 90%.[7,23] The results were not much different from Zaini's study. et al. at the Friendship Hospital obtained the sensitivity of plasma ctDNA in detecting EGFR mutations, namely 30%-40% with high specificity (83-96%).[8]

Liquid biopsy, especially plasma ctDNA, is an examination that has been recommended by the IASLC, CAP, and AMP into the guideline for molecular analysis in KPKBSK patients.[24] CtDNA examination is not recommended as a substitute for tissue/cytology examination, possibly because previous studies' sensitivity results still vary between low to moderate.[8,24] However, ctDNA examination is recommended in patients with CPBC with fewer cell counts than tissue/cytology specimens or in patients where tissue/cytology specimens are difficult to do, especially in advanced stages.[24]

The results of the positive predictive value (NPP) of ctDNA in this test were very high, namely 100%. These results indicate that a positive test result can indicate that patients with adenocarcinoma type KPKBSK have very high EGFR mutations detected. Meanwhile, the negative predictive value (NPN) of ctDNA in this test was relatively high, namely 80%. These results indicate a negative test result can predict that patients are not detected with high EGFR mutations. Thus, all lung cancer patients with positive EGFR mutations from ctDNA testing did have EGFR mutations. Based on the above studies' results, the detection of EGFR mutations in plasma is very likely to have a high predictive

value identical to mutations in tumors.[25]

There were no false-positive results in this study, where negative results from ctDNA tests were also negative on tissue/cytology examinations. In contrast, the results of this study showed 6 out of 42 patients with false-negative results, where the results of the ctDNA test were negative. Still, the tissue/cytology examination was positive for the detection of EGFR mutations. The absence of false-positive results is probably due to the lack of a tumor's heterogeneity. There is no difference in EGFR mutations between the tumor and the patient's plasma, or the tumor does not have a mutation (wild type).[23] The use of blood specimens as a source for examining EGFR mutations is limited by circulating cfDNA in the circulation. Doing so can result in a false-negative test result. Also, the volume of mutated DNA in the plasma is below the detection limit of the method used, leading to false negatives.[19]

Molecular examination to determine mutation status (including in the provision of targeted therapy) has become a routine examination in clinicians' daily practice.[26] Another advantage of ctDNA testing is that all DNA mutations from all tumors (including metastases) in the patient can be used as examination samples. This can reduce the risk of undetected EGFR mutations due to heterogeneity or an insufficient number of tumor cells.[7]

In the ASSESS study, it was found that ctDNA examination could be used to detect EGFR mutations that might be missed from tissue/cytology due to inadequate specimens obtained. However, ctDNA testing may not always detect EGFR mutations present in tumors even when the latest technology is susceptible.[7] Therefore, tumor tissue models remain the gold standard for detecting EGFR mutations before administering targeted therapy.[26]

Analysis of circulating tumor cells can only be performed on fresh blood specimens.[26,27] Several observational studies have found that the half-life of cfDNA in the circulation is between 16 minutes and 2.5 hours.[27] Ideally, the blood samples that have been taken should be checked for EGFR mutation detection in the laboratory. However, in our study, blood samples that have been taken by laboratory personnel are then sent out of town because the Real-Time PCR Scorpion-AMRS examination tool is not available, which is a weakness in our study.

CONCLUSION

The ctDNA examination has good accuracy with a sensitivity of 66.7% and a specificity of 100% in detecting EGFR mutations in adenocarcinoma lung cancer. The use of ctDNA is a promising alternative diagnostic examination if the tumor cell count in the tissue/cytology specimen cannot be used to detect EGFR mutations.

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ORIGINAL ARTICLE

Lung Function and Respiratory Symptoms of Petrol Station Attendants in Central and North Jakarta and Its Contributing Factors

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ABSTRACT

Background: To satisfy growing needs of petrol consumption in big city many new petrol stations has been built. Petrol station attendant is considered to have high risk exposure to dangerous pollutant from motor vehicle emission and petrol fumes, especially while filling up petrol tanks. Combination of those exhaust and petrol fumes is suspected to cause the reduction of lung function.

Methods: This research is a cross sectional study in petrol station in Central Jakarta and North Jakarta region between August 2017 and February 2018. A total of 97 petrol station attendants were taken in this research using consecutive sampling technique. The subjects were interviewed with questionnaires, spirometry and chest radiograph. Measurements of sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), ozone (O3), particulate matter 2,5 (PM 2,5) and steam gasoline (benzene) concentrations were performed at the study sites.

Results: In this study, 56.7% normal spirometry results, 42.3% abnormalities in the form of restriction, 1% obstruction and none of which experienced mixed disorders of restriction and obstruction. Most subjects (84.6%) did not experience respiratory complaints, 10.3% had a dry cough and 5.1% complained of cough with phlegm. There was a statistically significant association between peak expiratory flow and duration of work (p=0.011), but no significant association with other parameters such as forced vital capacity (FVC), %FVC, forced expiratory volume in the first second (FEV_1), %FEV_1 and the ratio of FEV_1/FVC.

Conclusion: Prevalence of lung function abnormalities of petrol station attendant is 43,3% and respiratory symptoms at 15,4% subject.

Keywords: lung function, petrol station attendant, respiratory symptoms.

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INTRODUCTION

DKI Jakarta as the capital of the Republic Indonesia which is also the centre of economy and trade recorded as having a crowded population. Based on data from the last Badan Pusat Statistik (BPS) in 2015, there were 10.177.924 inhabitants with a density of 15.367 people per km2. The large population is accompanied by increased purchasing power, leading to increased ownership of motor vehicles. The number of motor vehicles excluding military, police and diplomatic corps vehicles in Jakarta was recorded as 17,523,967 vehicles with annual growth of 9.93% over the last five years.[1]

The increase in the number of motor vehicles contributes importantly to air pollution levels in Jakarta. On a global scale, Jakarta ranks as the third-worst polluted city in the world after Mexico City and Thailand.[2] In 2012 it was reported that (particulate matter) in Jakarta had exceeded the threshold to reach 150 μg/m^3. Government Regulatory No. 41 the Year 1999 about Air Pollution Control states a clean air quality indicator that is when the maximum level of dust particles is 60 μg/m^3.[3] Environmental statistics in 1994 reported that 91.86% of air-polluting gas emissions in Jakarta came from the transportation sector. Other sources are from the industrial sector of about 5%, household activity 1.82% and garbage burning 1.29%.[4]

Emissions of exhaust gases of motor vehicles contain substances that harm health especially respiratoryhealth such as carbon monoxide (CO), sulfur dioxide (SO_2), nitrites dioxide (NO_2), hydrocarbons (HC) and particulate matter (PM_{10}). Data from Ministry of Health in 1999 showed levels of dust, SO_2 and NO_2 levels in Jakarta, Yogyakarta and Semarang as follows 280 μg/m^3, 0.76 ppm and 0.50 ppm. The figure is already beyond the standard of air quality.[4] Air Pollution Standard Index in 2003 from 6 monitoring stations in Jakarta showed the maximum daily concentration of CO, SO_2 and PM_{10} had exceeded the threshold.[5]

General refuelling stations in Indonesia are increasingly established to meet the needs of gasoline motor vehicles increasing. Some workers are tasked to serve the refuelling of motor vehicles with average work for 8 hours per day. Gas station attendant is a profession that has high risk exposed by the harmful pollutants that come from exhaust emissions of motor vehicles and gasoline vapor, especially when charging gasoline. The combination of exposure to vehicle

exhaust and gasoline vapor is thought to contribute from decreased pulmonary function test.[6,7]

In a study conducted by Hulke et al., about pulmonary function test on gas station attendants who have a working period of more than 5 years in the city of Bhopal, India reported that there is a pulmonary function disorder in the form of restrictions on gas station attendants.[8] Research by Begum et al., in the Indian city of Mysore on gas station workers who worked for more than 2 years also showed restriction disorder. This is seen from a significant decline in FEV_1 and FVC with a normal percentage of FEV1s.[6]

Dase et al., in Makasar city, Indonesia showed a decrease in vital lung capacity in 26 gas station attendants out of a total of 46 attendants examined. The decrease in vital capacity of the lungs has a significant relationship with age, working life and smoking habits.[9] This research will be conducted to find out the pulmonary function and respiratory complaints of gas station attendants in Central Jakarta, North Jakarta and the factors that contribute.

The aimed of this research are obtaining pulmonary function data and respiratory complaints from gas station attendant in Central and North Jakarta, and obtaining data on air quality in the general petrol gas station area of Central and North Jakarta.

METHOD

This research is a descriptive-analytic study using a cross-sectional study design. This research was conducted at gas stations in the Central and North Jakarta regions in August 2017 - February 2018. This research population is petrol station attendants who work in the area of Central and North Jakarta. The sample is an affordable population that meets the inclusion criteria. Sampling was taken using consecutive-sampling for each subject who completed the research criteria.

Inclusion criteria are petrol station attendants in Central and North Jakarta with a minimum working period of 1 year; and willing to take part in research and sign an informed consent. Exclusion criteria are petrol station attendants who have a history of pulmonary tuberculosis, suspected pulmonary TB, or are currently on medication; and gas station attendants who already have a history of asthma or COPD before working. Drop out criteria if respondents do not show up for examination or resign as subjects, respondents did not participate in part

of the planned tests, and respondents did not carry out all tests properly.

RESULT

This research is a cross-sectional study to find the prevalence of pulmonary function abnormalities and respiratory complaints among petrol stations attendants in Central and North Jakarta and determine the factors that influence it.

There were 97 subjects studied, mostly male. The characteristics of the research subjects, as shown in Table 1, include age, gender, body mass index, years of work, working hours in a week, wearing masks while working, and smoking habits.

The total research subjects' median age value was 25 years (range 19-42 years), with the proportion of the male sample being more than 72 people (74.2%). The median Body Mass Index (BMI) in the sample is 22 kg/m^2. It is included in the BMI classification of average body weight according to WHO Asia standards and the Ministry of Health's SKRT standards.

A total of 38.1% of study subjects did not smoke, and the remaining 61.9% of subjects smoked, with the most categories being in the mild Brinkman index of 55.7%. Only two subjects (2.1%) used masks during work. The median value of working time in the sample was 36 months (range 12-120), and the total working hours in a week was 48 hours (range 40-60 hours).

In this study, normal spirometry results were obtained in 55 study subjects (56.7%). Table 1 shows that spirometry abnormalities in the form of restriction were most commonly found in 41 subjects (42.3%), while one person only experienced obstruction, and none experienced a mixture of restriction and obstruction. Respiratory complaints in the form of dry cough were found in 10 subjects, cough with phlegm in 5 subjects, and no complaints in 82 subjects. There were no complaints of chronic cough and phlegm experienced by the research subjects. The mean spirometry results are shown in Table 1; FVC has a mean of 2868.4 ml with a standard deviation (SB) of 733.74 ml and a mean of percent CVP 81.6% with SB 15.06. The mean of FEV_1 was 2597.4 ml/second with an SB of 634.99 ml/second, while the mean of FEV_1/FVC was 90.8% with an SB of 5.58%. The peak expiratory current (PEFR) has a mean of 6.82 with SB 1.782.

This study found that the proportion of men who had pulmonary function abnormalities was higher than that of women whose spirometry was abnormal. The median age of subjects

with the abnormal pulmonary function was 26 years. The proportion of nonsmokers was smaller than the group with the mild Brinkman Index (IB). This study did not have subjects with severe IB. All subjects with spirometry disorders in this study did not wear masks when working.

Table 1. Distribution of Subjects According to Characteristics

Variable	Frequency	Mean±SD or Median (Min-Max)
Characteristic Subject		
Age*	-	25 (19-42)
Gender		
Male	72 (74,2%)	-
Female	25 (25,8%)	-
Body Mass Index*	-	22 (14-45)
The Use of Masks		
Yes	2 (2,1%)	-
No	95 (97,9%)	-
Working Period (month)*	-	36 (12-120)
Length of Work in a Week	-	48 (40-60)
Brinkman Index		
Nonsmokers (0)	37 (38,1%)	-
Mild smoker (1-200)	54 (55,7%)	-
Moderate smoker (201-600)	6 (6,2%)	-
Heavy smoker (>600)	0 (0,0%)	-
Test Results		
Spirometry		
Normal	55 (56,7%)	-
Obstruction	1 (1,0%)	-
Restriction	41 (42,3%)	-
Mix	0 (0,0%)	-
Respiratory Complaints		
Dry Cough	10 (10,3%)	-
Phlegm Cough	5 (5,1%)	-
No Complaint	82 (84,6%)	-
Spiro-metric Results		
FVC (ml)*	-	2868,6±733,74
%FVC*	-	81,6±15,06
FEV_1 (ml)*	-	2597,4±634,99
$\%FEV_1$*	-	84,1±14,82
FEV_1/FVC (%)*	-	90,8±5,58
APE*	-	6,82±1,782

Note: (*) Mean±standard deviation for normal distribution; median (minimum-maximum) for abnormal distribution

In the statistical analysis as shown in Table 2, it can be seen that there is no significant relationship between the independent variables consisting of gender, age, Body Mass Index (BMI), IB, use of masks, length of work in months, duration of working hours in a week with spirometry abnormalities after going through statistical testing (P>0.05).

Each spirometry parameter was then analyzed for its relationship to years of service. A significant relationship was obtained between PEFR and working period with a P=0.011, as shown in Table 3. Still, there was no significant relationship between parameters of FVC, %FVC, FEV_1, and $\%FEV_1$ with years of service. There was a tendency for a relationship between the FEV_1/FVC ratio and tenure but did not exceed the statistical significance limit of 0.05.

Table 3.Relationship between spometric parameters and working period

Parameter	P
FVC	0,274
%FVC	0,433
FEV_1	0,384
$\%FEV_1$	0,465
FEV_1/FVC	0,083
APE*	0,011*

Note: P<0,05 statistically significant

Table 2. The relationship between independent variables and spirometric abnormalities

Subject Characteristics	Abnormal Spirometric	Normal Spirometric	P	CI 95%
Gender				
Female	12	13	0,774	0,310-1,9
Male	30	42		
Age	26 (19-42)	24 (19-39)	0,51	
Body Mass Index	22 (14-45)	22 (17-41)	0,261	
Brinkman Index				
Nonsmokers	18	19	0,341	
Light smoker	23	31		
Moderate smoker	1	5		
Heavy smoker	0	0		
The Use of Masks				
Yes	0	2	0,504	
No	42	53		
Working Period (month)	48 (18-120)	36 (12-108)	0,127	
Length of Work in a Week	48 (40-60)	48 (40-60)	0,148	

Table 4. The relationship between independent variables and respiratory complaints

Subject Characteristics	Respiratory Complaints			P
	No Cough	Dry Cough	Phlegm Cough	
Gender				0,063
Female	24	1	0	
Male	58	9	5	
Age				0,487
Body Mass Index				0,763
Smoking Habit				0,572
Not a smoker	33	3	1	
Former smoker	3	1	0	
Active smoker	46	6	4	
Brinkman Index				0,385
Nonsmokers	33	3	1	
Mild smoker	45	5	4	
Moderate smoker	4	2	0	
Heavy smoker	0	0	0	
The Use of Masks				0,544
Yes	2	0	0	
No	80	10	5	
Working Period (month)				0,085
Length of Work in a Week				0,672

This study found that male subjects had more respiratory complaints in dry cough and phlegm than female subjects. However, there was no statistically significant relationship between sex and respiratory complaints. Statistical analysis between the variables of age, BMI, IB, use of masks, length of work in months, and hours of work in a week with respiratory complaints variables also found no statistically significant relationship. The relationship between the demographic independent variable and the respiratory complaint variable is shown in Table 4.

This study involved samples from several gas stations in Central Jakarta and North Jakarta. At the Yos Sudarso gas station, the subjects with lung function abnormalities were five attendants, while the normal ones were 15 attendants. Most of the Pegangsaan gas station attendants showed normal spirometry results, namely 11 subjects, while only 3 subjects had spirometry abnormalities. In contrast to the results obtained at the Pegangsaan gas station, at the Abdul Muis gas station, most gas station attendants had pulmonary function disorders, namely 13 attendants.

Table 6. Air quality at the study site

Gas Station Location	NO_2 (≤0,2 ppm)	SO_2 (≤2 ppm)	O_3 (≤0,1 ppm)	CO (≤25 ppm)	PM2.5 (≤3 mg/m^3)	Benzene (≤0,5 ppm)
Pramuka	<0,017	<0,022	0,012	22	0,008	0,198
Cikini	0,019	<0,022	0,010	20	0,014	0,144
Abdul Muis	0,052	<0,022	0,009	8	0,013	<0,092
Yos Sudarso	0,058	<0,022	0,007	10	0,025	<0,092
Pegangsaan	0,022	<0,022	0,007	6	0,041	0,174

In comparison, the normal ones were only five attendants. At the Cikini gas station, seven attendants showed abnormal spirometry results, and 13 attendants had normal spirometry results, while 14 attendants at Pramuka gas station had spirometry abnormalities and 11 attendants without spirometry disorders. Based on this research, the gas station attendants who experienced the most lung function disorders were at Abdul Muis and Pramuka gas station. These results are shown in Table 5.

Table 5. Distribution of spirometry results based on the gas station location

Location Gas Station	Spirometry Results	
	Abnormal	Normal
Yos Sudarso	5	15
Pegangsaan	3	11
Pramuka	14	11
Cikini	7	13
AbduL Muis	13	5

This study also measures the air quality, including gas levels of NO2, SO_2, $O3$, CO, and $PM_{2.5}$. NO_2 gas showed the highest level at the Yos Sudarso gas station (0.058 ppm), but this level was still below the threshold value (TLV), namely ≤0.2 ppm. SO_2 levels at all the gas stations studied showed <0.022 ppm, far below TLV (≤2 ppm). The highest O_3 level at Pramuka gas stations is 0.012 ppm, but this level is still below TLV. CO levels at the Pramuka gas station 22 ppm and Cikini 20 ppm showed levels that almost passed TLV (≤25 ppm). Benzene levels at all gas stations are still safe, the highest at Pramuka gas stations at 0.198 ppm, while the $PM_{2.5}$ levels at all research locations were far below TLV. These results are shown in Table 6.

DISCUSSION

This research was conducted from August 2017 to February 2018, aiming to determine lung function and respiratory complaints and the factors that influence gas station attendants spread across five gas stations in Central Jakarta and North Jakarta. Petrol station attendant who are the research subjects have a working period between 12 to 120 months with

a median of 36 months and 48 hours of work a week. Only two gas station attendants use masks while working. Complaints of cough were found in 15 attendants (15.5%) and phlegm in 18 gas station attendants (18.6%), but these respiratory complaints have not been experienced chronically. Spirometry abnormalities were found mainly in the form of restrictions, namely in 41 attendants (42.3%), obstruction only in 1 officer (1%), and none of them experienced mixed restriction and obstruction.

The age characteristics of the study subjects had a median age of 25 years with the youngest age of 19 years and the oldest age of 42 years. The age data in previous research has a normal distribution so that it uses the average age. Research by Zafar in Karachi city, Pakistan has the average age of the study subjects 29.89 years with a standard deviation of 10.72 years.[10] other studies in Lucknow city, North India showed the average age of similar gas station attendants was 30.6 years with a standard deviation of 11.34 years.[11] Gender in this study subject was 72 men (74.2%). This is similar to research conducted by Adeniyi in Nigeria, involving 73 male subjects (73.7%) and 26 female subjects (26.3%).[12]

Nutritional status is assessed based on Body Mass Index (BMI). In this study, abnormal data distribution obtained a median BMI of 22 kg/m^2 with a low value of 14 kg/m2 and a top of 45 kg/m^2. Anuja et al., in Chennai city, India found an average BMI of 22.14 kg/m2 with a standard deviation of 3.04 kg/m2 at gas station attendants who became study subjects.[13] The average BMI result was similarly found by Choudhari et al., in Aurangabad other cities in India amounting to 20.46 kg/m2 with a standard deviation of 2.22 kg/m2.[14]

A total of 60 research subjects (61.9%) have a smoking habit with a mild Brinkman index category of 55 attendants (55.7%), while as many as 6 people (6.2%) and there is no which is in the category of Brinkman severe index. This is in contrast to the results of research in Nigeria by Adeniyi et al., that showed gas stations that do not smoke more are 96%. Research in Zambia also showed 176 non-smoking study subjects gas station attendant (92.6%) while those who smoked only 14 attendants (7.4%). The results of this different study are estimated because in most workers in Asian countries show a high prevalence of smokers.[15]

Gas station attendants who sampled the study had a median

working period of 36 months with a maximum working period of 12 months and the longest of 120 months while the median duration of work in 48 hours a week. The shortest work duration in a week was found to be 40 hours and the longest 60 hours per week. Similarly, Adeniyi et al., research found gas station workers with a median working life of 30 months with a new working period of 12 months and the longest 360 months.[12] Nothing yet other studies that analyze the variable duration of work within a week as done in this study.

Alam et al., in Pakistan reported research subjects with working duration categories of <8 hours per day, 8-12 hours per day and >12 hours per day. Most research subjects worked >12 hours per day on the study. The results showed there were significant differences in lung vital capacity (VC) between research subjects working <8 hours per day, 8-12 hours per day and >12 hours per day with P=0.029.7.[16] Masks as Personal Protective Equipment (PPE) on most research subjects (97.9%) not used. Other studies have only reported that most gas station officials do not use masks during work but do not make them one of the variables in the study to be analyzed.[10,17]

Spirometry examination in this study uses Pneumobile Indonesia as a reference. Spirometry abnormalities were found in 42 subjects of the study consisting of 41 attendants (42.3%) restrictions and 1 officer (1.0%) obstruction. More than half of the study subjects showed normal spirometry results of 55 attendants (56.7%). The results were similar to Shonga et al., studies in Zambia that reported normal pulmonary lung function in 71% of gas station attendant studied, restrictions experienced by 29% of subjects and none experienced obstruction.[18] Other research by Solanki et al., in India showed restrictive abnormalities in 14% of study subjects while obstruction on only 1% of subjects.[17] An in vivo study in experimental mice found persistent exposure to gasoline vapor can decrease lung restriction due to reduced surfactant levels.

The Forced Vital Capacity in this study had an average of 2868.4 ml with a standard deviation (SD) of 733.74 ml. These results are in contrast to research conducted by Kesavachandran et al., in India which found an average FVC of 3260 ml with a SB of 670 ml.[11] The higher average FVC may be due to the characteristics of the subjects in the study in India as entirely male while in the study we conducted involved 25 female gas station attendants (25.8%).

This certainly affects the value of FVC because the lung capacity of men is greater than that of females. Average percent of FVC earned in our research is 81.6% with a default deviation of 15.06%. Adeniyi et al., in Nigeria reported a similar average FVC percent of 83.4% with an SB of 12.2%.[12]

The study showed an average FEV_1 of 2597.4 ml/s with an SB of 634.99 ml/s and 84.1 percent FEV_1 with an SB of 14.82%. Similar results were reported in the Adeniyi et al., studies which averaged FEV_1 2900 ml/s with SB 700 ml/s and percent FEV_1 81.8% with SB 16.1%.[12] The FEV_1/FVC average in our research is 90.8% with SB 5.58%. Research by Bhide et al., in India showed a similar yield of 94.56% with SB 10.09%. Peak Expiratory Flow Rate of the subject of this study shows average of 6.82 liters/second with SB 1,782 liters/second is similar to Bidhe et al., 5.6 liter/s with SB 2.1 liter/s.[19]

The study found the majority of gas station attendants were male. This is in accordance with the research of Bhide et al., Dube et al, Solanki et al., in India whose attendants are all male and Adeniyi et al., research in Nigeria which shows 73.7% of gas station attendant are dominated by men.[12,17,19,20] Proportion of male gas station attendants who have pulmonary lung function disorders more than women however is not found significant get a relationship between the gender with abnormalities in spirometry. In this study there was no significant relationship between Brinkman Index and spirometry disorder. These results are similar to Ezejindu et al., studies in Nigeria that found no relationship relationship (P=0.514) between smoking habits and APE which is one of the parameters of spirometry.[21]

The study found the length of work within a week with a median of 48 hours in both subjects with spirometry abnormalities and normal. These length of work variables have no significant relationship with spirometry abnormalities. These results are similar to Alam et al., studies in Pakistan is analyzing the relationship between spirometry parameters and the length of work per day. The results showed there was no significant relationship between spirometry parameters are FVC, FEV_1 and APE with research subjects working <8 hours per day, 8-12 hours per day and >8 hours per day.[16]

In this study, there was a longer working period in the study subjects that had spirometry abnormalities, but there was no significant relationship between working time and spirometry disorder. These results are consistent

with all three studies performed by Kesavachandran et al, Aprajita et al., and Dube et al., in India which showed that there were spirometry abnormalities in subjects with longer working period even though the studies found a significant relationship. This difference in meaning is likely due to large differences in samples and differences in length of working period.[11,20,22]

In the spirometry parameter there is a significant relationship between the working period and PEFR (P=0.011) but no significant relationship is found between the working period and the FVC parameter, %FVC, FEV_1, $\%FEV_1$, FEV_1/FVC. Research by Anuja et al., in India also shows a significant relationship between working period and APE with P=0.021. Another study in India by Dube et al., also found that the longer the subject's working period the PEFR scores would decrease.[20,23]

This study subjects found who had complaints of cough or phlegm respiratory were 14 male subjects and this was more than female subjects. However, no significant relationship was found between the gender and respiratory complaints. Statistical analysis between age variables, BMI, IB, the use of masks, the length of work in months and working hours in a week with variable respiratory complaints also found no statistically significant relationship. Research by Zafar et al., in Pakistan found cough complaints in 80.7% of study subjects showed significant differences when compared to controls. This may be due to differences in the length of time worked and differences in the number of samples.[10]

This study uses the design of cross-sectional research that has a weakness in looking at causal relationships due to the data retrieval of risk factors and effects carried out at the same time. This design is chosen based on consideration time, effort and funds available. Sampling requires the suitability of the time with the work schedule of the gas station attendant which is divided into 3 schedules namely morning, noon and night. Obstruction prevalence is only obtained on one subject so it cannot be further analyzed. Measurements of air quality performed at each gas station could not directly assess the relationship between pulmonary function disorders that occurred in the study subjects with exposure to air pollution and gasoline vapor because they were not measured Individually.

CONCLUSION

There is no significant relationship between age and pulmonary lung

fucntion abnormalities and complaints respiratory. There is no significant relationship between gender with abnormalities of the physiology of the lungs and respiratory complaints. There is a significant relationship between the PEFR parameters and the working period of the research subject but there is no significant relationship with the other spirometry parameter.

There is no significant relationship between long working in a week with pulmonary function abnormalities and respiratory complaints. There is no significant relationship between the use of PPE when working with pulmonary function disorders and respiratory complaints. There is no significant relationship between nutritional status and pulmonary disorder and respiratory complaints. There is no significant relationship between smoking status with abnormalities of the physiology of the lungs and complaints of respiratory. Gas levels of NO_2, CO, SO_2, O_3 and $PM_{2.5}$ at research site gas stations are below the threshold value.

Further research is needed in a cohort regarding the factors affecting pulmonary function in gas station attendant. In the next research, it is necessary to check surfactant levels to prove the cause of restrictions on gas station attendants.

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ORIGINAL ARTICLE

The Effect of Two-Mile Jogging Training on Lung Function Values in TNI Soldier Kodam I/Bukit Barisan

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ABSTRACT

Background: Military soldiers are army personnel who are required to have good physical endurance and optimal fitness, include. So, it's needed physical exercise, include to be able to improve lung function. One parameter that can reflect physical fitness are lung function and VO_2max. This study aims to determine whether there is a relationship between physical exercise in the form of 2-mile jogging with increased lung function and VO_2max of military soldiers Kodam I Bukit Barisan

Methods: This research is an experimental study carried out in February-April 2019 against the TNI soldiers of the Bukit Barisan Military District I. The research subjects were divided into two groups, group 1 who underwent regular 2-mile jogging exercises 3-5 times a week with a duration of 25 minutes for 2 months, and group 2 who underwent non-routine jogging exercises (less than 3 times a week). Lung function was assessed by spirometry.

Results: As many as 68 military soldiers were involved in this study which were divided into two groups, 38 people in the group 1 who routinely trained and 30 people in group 2 that did not routinely practice. Group 1 FEV_1 values were higher than group 2 (P=0.03). No significant differences in terms of FVC, MVV and VO2max in both groups. Lung function of smokers were lower than non-smokers, but not statistically significant.

Conclusion: There were significant differences in FEV_1 values between military soldiers who routinely and did not routinely undergo 2-mile jogging exercises.

Keywords: jogging exercise, spirometry, lung function

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INTRODUCTION

Indonesian National Army Soldiers (TNI) are army personnel prepared for military careers to ensure the security of military organizations and communities. To carry out his duties, a Soldier of the TNI demands to have good physical endurance and optimal fitness (physical fitness). The essential elements in physical fitness are cardiorespiratory endurance, which is the ability of the heart and lungs and blood vessels to function optimally in a state of rest as well as exercise for taking in oxygen and then distribute it to tissues in the metabolic processes of the body.[1]

One way to assess fitness in physical activity is to measure the value of pulmonary function and maximum oxygen capture value or VO_2max. Physical exercise is essential for maintaining and improving physical fitness. Aerobic physical exercise is able to optimize heart performance to increase blood capacity to transport and distribute oxygen to tissues to meet metabolic needs.[1,2]

This form of jogging exercise is one of the aerobic exercises that has been validated to assess the cardiovascular endurance of healthy people[3], who in this case are TNI soldiers. This research aims to find out whether there is a relationship between physical exercise in the form of jogging with increased lung function and uptake maximum oxygen to the soldiers of the TNI Kodam I Bukit Barisan.

METHOD

This research is an experimental study design with two group pretest-posttest conducted in February – April 2019. The research subject is the soldier TNI Kodam I Bukit Barisan, which is distinguished into 2 groups which taken by using a consecutive sampling technique.

Group 1 is a TNI soldier who undergoes regular training. The form of exercise is jogging 3 – 5 times a week, with a duration of 25 minutes/training session. The training program is carried out for 2 months. As for the group 2 is TNI soldiers who undergo regular training, which is less than 3 times a week.

Measurement of lung function and maximum oxygen capture value is done before and after the exercise program. Lung function is measured through spirometry examination using two manoeuvres, namely FVC manoeuvres, to obtain FEV_1, FVC and FEF_1/FVC values. A second manoeuvre follows the examination, the MVV manoeuvre to get an MVV value that represents the strength of the breathing muscles.

Table 1. The Characteristic of the Subject

Characteristics	Routine		Not Routine		P*
	n	%	n	%	
Gender					
Male	38	100.0	27	100.0	---
Female	0	0.0	0	0.0	
Age					
<40 old	37	97.4	15	55.5	<0.01
≥40 old	1	2.6	12	45.5	
BMI					
Underweight	0	0.0	0	0.0	
Normoweight	12	31.6	4	14.8	0.17
Overweight	11	28.9	9	33.3	
Obese	15	39.5	14	51.8	
Cigarette					
No Smoking	17	44.7	16	59.3	
Low	7	18.4	4	14.8	0.34
Medium	14	36.8	7	25.9	
High	0	0	3	10	
%FEV_1					
≥80	16	42.1	12	45.5	
50-79	22	57.9	15	55.5	0.88
30 49	0	0.0	0	0.0	
<30	0	0.0	0	0.0	
%FVC					
≥80	20	52.6	13	48.1	
50-79	18	47.4	14	52.9	0.51
30-49	0	0.0	0	0.0	
< 0	0	0.0	0	0.0	
%FEV_1/FVC					
≥75	38	100.0	27	100.0	---
<75	0	0.0	0	10.0	
%MVV					
≥80	2	5.3	2	7.4	0.82
50-79	28	73.7	19	70.3	
30-49	8	21.1	6	22.2	

Note: (*) Test Chi Squared. BMI=Body Mass Index, FEV_1=First second forced expiration volume, FVC=Forced vital capacity, MVV=Maximal Voluntary Ventilation.

This formula has been shown to have a good level of accuracy to measure the value of maximum oxygen uptake in a healthy Indonesian population. Pulmonary function treatment is carried out before and after the training program for 2 months. The data obtained is then done statistical analysis with a different mean test using statistical package for social sciences (SPSS) software where the value of P<0.05 is stated to mean.

RESULT

A total of 68 TNI soldiers were involved as subjects in this study, which was distinguished into two groups, namely a group with a jogging routine of 38 people, and a group that underwent a non-routine jogging exercise of 30 people. All research subjects are male.

The characteristics of this study subject can be seen in Table 1. The preliminary examination results of the lung function of both groups can be seen in Table 2. It can be seen that there was a significant difference in FEV_1/FVC scores at the beginning of the study between the two groups, where the group that did not regularly undergo exercise had a lower FEV_1/FVC score than the group that was a regular exercise. However, FEV_1/FVC values in both groups are still within the normal value range (>75%).

Table 2. The results of the examination pulmonary function before the exercise (Baseline)

Parameters	Mean±SD		P
	Routine	Not Routine	
Before Exercise			
FEV_1 (%)	78.2±8.33	74.9±9.27	0.12
FVC (%)	78.7±8.06	76.4±10.3	0.3
FEV_1/FVC (%)	82.2±4.35	79.3±4.69	0.01*
MVV (%)	57.1±11.9	57.1±12.0	0.98
After Exercise			
FEV_1 (%)	78.7±8.3	74.9±7.7	0.04*
FVC (%)	78.9±6.5	76.2±7.9	0.12
FEV_1/FVC (%)	82.2±6.1	81.3±4.3	0.08
MVV (%)	59.7±11.2	58.8±15.3	0.69
VO_2max	55.9±4.6	58.0±5.0	0.07

Note: (*) T Independence test, FEV_1=First second forced expiration volume, FVC=Forced vital capacity, MVV=Maximal Voluntary Ventilation

All subjects performed aerobic exercises in the form of jogging for 2 months. Group 1 did jog 3 – 5 times a week, with a duration of 25 minutes/training session, while group 2 did less than the amount of physical exercise, and was grouped as a non-routine group. After the 2-month training program is completed, pulmonary faal examination and max VO_2 assessment are carried out on all research subjects with the following results.

Table 2 shows that there is a significant difference in FEV1 values and FEV_1/FVC values between groups undergoing regular jogging exercises and those who did not routine ($P<0.05$). The group who regularly underwent exercise had higher FEV_1 and FEV_1/FVC scores compared to those who did not exercise regularly. However, there are no significant differences in terms of FVC, MVV or VO_2max.

DISCUSSION

Physical exercise is defined as body movements produced by skeletal muscles that cause energy to be used. Physical activities in daily life can be categorized into work, sports and daily activities. Exercise is a part of physical activity that is planned, structured and repetitive and has the ultimate goal of improving or maintaining physical fitness[4]. Many studies recommend treadmill aerobic exercise or jogging as a way to maintain or improve lung function[5].

Physical exercise will cause your muscles to get stronger. Improvement in muscle function is found, especially the respiratory muscles and will cause breathing to be more efficient, especially at rest. Pulmonary ventilation in people who regularly exercise and people who don't exercise is the same, but people who regularly exercise can breathe more slowly and deeply. This causes the oxygen needed for muscle work in the ventilation process to decrease so that with the same amount of oxygen, the respiratory muscles of people who regularly exercise will work more effectively[6].

In one study, 6790 subjects were followed for 19 months. Those undergoing regular physical exercise showed 50 ml increases in FEV_1 and 70 ml in CVP; In contrast, subjects who rarely exercised had a 30 ml decrease in FEV_1 and a 20 ml decrease in CVP. These findings are consistent with other studies, which suggest that FEV_1 improvements are mainly due to the expansion of the lungs during high-intensity aerobic exercise, resulting in a greater volume of air being introduced into the airways and widening of the airways[5]. This study also found the

same thing. There was a significant increase in the FEV_1 value in the group who routinely underwent *jogging* exercise compared to those who did not exercise regularly (78.7% vs 74.4%; P<0.05).

The results obtained in this study are slightly different from the findings of Rawashdeh et al. This study showed that there was no significant difference between the group who regularly exercised and those who did not regularly (59.7% vs 58.4%; P=0.71). The difference in the results of this study could occur because the TNI soldiers who were the sample of the study were healthy people, so the difference in the effect of training was not as straightforward as those found in patients with COPD.[6,7]

MVV is a measure of the performance of the respiratory muscles. The increase in MVV after exercise can be due to the increase in respiratory muscle development associated with physical activity. MVV elevation without an increase in CVP indicates the effect of exercise on the respiratory muscles occurring without an increase in large or small airways because MVV is less affected by the state of the airways than other parameters. A higher exercise intensity or longer duration may be required to influence pulmonary function parameters such as CVP and MVV[8].

CONCLUSION

There is a significant difference in the FEV_1 value between TNI soldiers who routinely and do not routinely undergo jogging training. There is no relationship between jogging exercise and the FVC and MVV values.

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ORIGINAL ARTICLE

Rate Between Examination of EGFR Mutation Blood Plasma Sample (ctDNA) With Cytological/Histopathological Sample in Adenocarcinoma Lung Cancer

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ABSTRACT

Background: Most adenocarcinoma lung cancer which is found at an advanced stage with cytology / histopathological samples is hardly available. Examinations EGFR mutations as a biomarker for adenocarcinoma lung cancer using cytological/histopathological sample (tissue biopsy or resection and cytologi) and ctDNA blood plasma. Examination of EGFR mutations in ctDNA blood plasma sampling is simpler and easier, which also can be used as predictive and prognostic markers in non-small cell carcinoma lung cancer patients. The purpose of this study is to determine and analyse the degree of compatibility between examination of EGFR mutations by blood plasma (ctDNA) samples with the examination of cytology/histopathological EGFR mutations in adenocarcinoma lung cancer.

Methods: Diagnostic test research, by taking medical records of patients with adenocarcinoma lung cancer from January to September 2019 at Dr. Moewardi Surakarta, who was examined by EGFR mutations in cytology / histopathology and ctDNA samples.

Result: The Subjects of this study were 73 patients with adenocarcinoma lung cancer. The level of compatibility of ctDNA with EGFR mutations in cytology/histopathology samples was categorized as moderate and statistically significant (Kappa=0.459; P=0.0001), with a sensitivity value of 54.5% and a specificity of 90%.

Conclusion: The high/moderate concordance between the different DNA sources for egfr mutations (cytology/histopathology) and ctDNA.

Keywords: lung cancer, adenocarcinoma, EGFR, ctDNA

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INTRODUCTION

Non-small cell carcinoma lung cancer is the leading cause of cancer-related death. Lung cancer cases are found at an advanced stage due to non-specific symptoms (57% of lung cancer cases in the US are detected by metastasis). Pulmonary adeno-carcinoma represents about 50% of lung cancers and 60% of LCMC. EGFR examination becomes a routine test after the diagnosis of pulmonary adenocarcinoma has been established for the selection of patients receiving tyrosine kinase inhibitors (TKIs). EGFR mutation examination samples derived from tissue biopsy/resection and cytology are often not available because tumor biopsy is an invasive and high-risk procedure. Liquid biopsy can detect biomarkers associated with tumors to diagnose lung cancer earlier and more safely.[1–7]

The ASSESS study in the subset of Spanish patients, the good concordance (almost 90%) between the different DNA sources supports the use of plasma samples when tumor tissue is not available. Zhang et al's study about ctDNA assessment of EGFR mutation status in Chinese patients with advanced non-small cell lung cancer in real-world setting conclude ctDNA based EGFR mutation test is feasible and could be a surrogate when tissue biopsy is not available.[1–7]

The purpose of this study was to determine and analyze the degree of concordance of the EGFR mutations examination originating from blood plasma samples (ctDNA) with examinations derived from cytology /histopathology. This study hope to be able to provide scientific information regarding the concordance of EGFR mutations examination originating from blood plasma (ctDNA) with cytology/histopathology samples and as basic data for further research.

METHOD

This research is a diagnostic test research. The study population was all lung cancer populations with adenocarcinoma types, naïve treatment. The diagnosis was confirmed by the presence of lung mass images on CT-scans and cytology/histopathology examinations were performed for both primary tumours and metastatic lesions and EGFR mutations were examined from cytology/histopathology samples and blood plasma (ctDNA) who underwent outpatient and inpatient care at Dr. Moewardi Surakarta from January-September 2019.

The inclusion criteria is patients with adenocarcinoma lung cancer, the diagnosis is confirmed by the presence

of lung mass images on CT-scan and cytology/histopathological examination of both primary tumors and metastatic lesions with adenocarcinoma results, which are subjected to ctDNA examination and examination of EGFR mutation cytology/histopathology. The exclusion criteria are the patient's medical records are missing or incomplete, examination of EGFR mutations is performed in only one of the two tests for EGFR mutations (examination of EGFR mutations from cytology/histopathology only, or blood plasma ctDNA only). The sample of this study were obtained from the medical record data of adenocarcinoma lung cancer patients at Dr. Moewardi Hospital.

Examination of EGFR mutations with cytological samples (pleural effusion, bronchus rinse, bronchial swab, FNAB) or histopathology fixed with a neutral buffer of 10% formalin on cell blocks or slides stained / not stained with tumor cell counts greater than 200 cells and containing more From 50% tumor cells, both primary and metastatic lesions using the DNA extraction method with the Qiagen QIAamp® DNA Micro kit, mutation analysis using PCR HRM, fragment analysis, direct sequencing and amoyDx. 100% specificity. ctDNA examination using Therascreen EGFR Plasma RGQ PCR Kit.

Sample criteria were plasma EDTA from adenocarcinoma positive patients. Minimum plasma volume of 4.5 ml. One job can be done up to a maximum of 16 samples or 1 kit can be divided by 3x runs with samples per one run. Plasma sample separation and storage procedures prior to EGFR examination was fresh blood samples should be centrifuged immediately to separate the plasma within 2 hours if stored at room temperature or 8 hours if stored at 4^{o}C. Fresh blood centrifuge at 2000x g for 10 minutes. Separate the plasma into a new tube. The separated plasma can be stored at -20^{o}C for 4 weeks or -80^{o}C for longer storage. Avoid re-freezing. Only thaw if an examination is to be performed. Thaw the plasma at room temperature on the day of the EGFR examination. Centrifuge a second time at a speed of 16,000 x g for 10 minutes at 4^{o}C (at fixed angle rotor). Separate the clear portion of the plasma into a 14 ml sample tube (14 ml Falcon® polystyrene 17 x 100 mm round bottom tube (BD, paint no. 352051)) to continue the extraction process. Ethical clearance approved by The Health Research Ethics Committee Dr. Moewardi General Hospital.

Data analysis was performed using SPSS 21 for Windows. In this

study, the analysis is presented with a frequency distribution and percentage. The degree of concordance between the results of the EGFR mutation examination with blood plasma samples (ctDNA) and cytology/histopathology samples was calculated by means of a test of agreement (Kappa Cohen) with kappa values:> 0.8 (very good suitability), kappa: 0.6 - 0.8 (good suitability), kappa: 0.4 - 0.6 (moderate suitability) and kappa: <0.4 (less suitability). The degree of concordance between ctDNA examination results and EGFR mutations (cytology/ histopathological samples) is presented in the 2x2 table. We calculate sensitivity, specificity, positive and negative predictive value.

RESULT

The research was conducted in the medical record room of Dr. Moewardi Surakarta from October 2019 to November 2019. The results of recording the medical records of patients with adenocarcinoma lung cancer that were carried out by EGFR examination were obtained from cytology/histopathology and blood plasma (ctDNA) samples from both primary tumors and metastatic lesions obtained by 73 people. The scheme sample collection is on Figure 1.

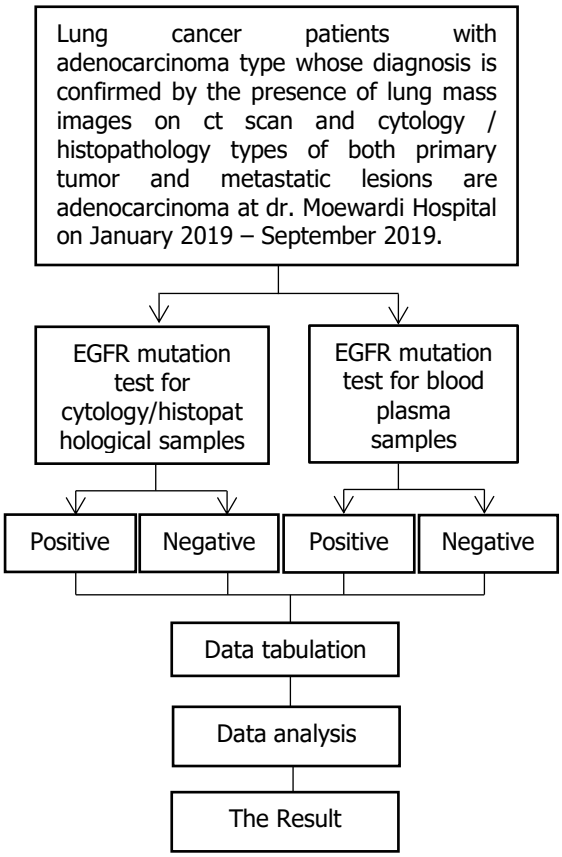

Figure 1. The scheme of sample collection

Lung cancer patients with adenocarcinoma types based on the table above were 35 men (47.9%) and 38 women (52.1%). The majority of patients with adenocarcinoma lung cancer in the study were ≥40 years by 67 people (91.8%), while the rest <40 years were 6 people (8.2%).

Table. 1 Basic characteristics of research subjects

Characteristics	Frequency	Percentage
Gender		
Male	35	47.9
Women	38	52.1
Age		
<40 years	6	8.2
≥40 years	67	91.8
EGFR Mutation Results		
No mutations	39	53.4
Del Exon 19	18	24.7
Exon 21 L861Q	1	1.4
Exon 21 L858R	10	13.7
Exon 20 T790M + Exon 21 L858R	1	1.4
Del Exon 19 + Exon 21 L858R	2	2.7
Exon 21 L858R + Exon 21 L861Q	2	2.7
ctDNA results		
No mutations	48	65.8
Del Exon 19	16	21.9
Exon 21 L858R	7	9.6
Exon 20 T790M + Exon 21 L858R	2	2.7
Smoking History		
Yes	30	41.1
Not	43	58.9
Stadium		
IIIC	4	5.5
IV	69	94.5
Metastasis		
There is no	4	5.5
Pleural effusion	25	34.2
Bone metastasis	6	8.2
Metastatic liver	3	4,1
Brain metastasis	2	2.7
Pneumonic type	3	4,1
Pleural effusion, bone, liver metastases	5	6.8
Pleural effusion, bone metastasis	8	11
Pleural effusion, bone, brain metastasis	1	1.4
Pleural effusion, colli lymphadenopathy	2	2.7
Bone, brain metastasis, pneumonic type	2	2.7
Bone metastases, colli lymphadenopathy	1	1.4
Bone metastasis, pneumonic type	2	2.7
Pleural effusion, liver metastases	5	6.8

Characteristics	Frequency	Percentage
Bone, liver metastases	3	4,1
Bone, brain metastasis	1	1.4
Cytology / Histopathology Samples		
TTNA	40	54.8
Bronchial brushing	7	9.6
Bronchial washing/BAL	4	5.5
Endobronchial biopsy	6	8.2
FNAB	7	9.6
Thoracocentesis	8	11.0
Core Needle Biopsy	1	1.4

The results of ctDNA examination were obtained as follows, there were no mutations in 48 people (65.8%), 16 people with exon 19 deletions (21.9%), 7 people with exon 21 L858R (9.6%), 20 T790M exon. + Exon 21 L858R there are 2 people (2.7%). Smoking history was also found on the patients there were 30 people (41.1%) smoked while 43 people (58.9%) did not smoke. The stage in the subjects of this study was an advanced stage, there were 4 people (5.5%) with stage IIIC, while in stage IV there were 69 people (94.5%).

The table above also shows that 4 patients (5.5%) had no metastases, while the other 69 patients had metastases (94.5%). Pleural effusion occurred in 25 people (34.2%), this is the most common metastasis in the subjects of this study. Table 1 shows that the metastases that occurred in the subjects of this study did not only occur in one place but there were also several places such as pleural effusion, bone metastasis and brain metastasis simultaneously.

Table 2. Results of EGFR mutations in cytological/histopathological samples by sex

Sex	EGFR Mutation Results		Total
	Negative	Positive	
Male	23 (31.5%)	12 (16.4%)	35 (47.9%)
Women	17 (23.3%)	21 (28.8%)	38 (52.1%)
Total	40 (54.8%)	33 (45.2%)	73 (100%)

The result of EGFR mutations based on cytology/histopathological samples based on sex was more prevalent in 21 women (28.8%) compared to men, namely 12 (16.4%) shown in Table 2.

Table 3. Results of ctDNA by sex

Sex	ctDNA results		Total
	Negative	Positive	
Male	27 (37.0%)	8 (10.9%)	35 (47.9%)
Women	21 (28.8%)	17 (23.3%)	38 (52.1%)
Total	48 (65.8%)	25 (34.2%)	73 (100%)

Table 4. Kappa test results between ctDNA and EGFR mutation examination of cytology / histopathology samples

CTDNA	EGFR mutations		Total	Kappa test	P
	Positive	Negative			
Positive	18	4	22	0.459	0.0001
Negative	15	36	51		
Total	33	40	73		

Table 5. Sensitivity and specificity tests

ctDNA	EGFR mutations		Total
	Positive	Negative	
Positive	18	4	22
Negative	15	36	51
Total	33	40	73
Sensitivity	: 0.545	Specificity	: 0.900
PPR	: 0.818	NEV	: 0.706
PLR	: 5,450	NLR	: 0.505

Note: PPR=Positive Probability Ratio, NEV: Negative Estimated Value, PLR: Positive Likelihood Ratio, NLR: Negative Likelihood Ratio

The results of ctDNA examination based on sex in Table 3 show that there were more mutations in 17 women (23.3%) while in men there were 8 people (10.9%). The ctDNA examination compared with EGFR mutations with cytology/histopathology samples is called true positive taking into account the same mutation points. The kappa test results show a value of 0.459 which means the level of concordance between the results ctDNA with EGFR examination of cytology/histopathological samples with moderate levels, P=0.0001 (P<0.05), which means that the suitability of ctDNA with cytology/histopathology was statistically significant.

The diagnosis of EGFR mutations with ctDNA samples obtained a sensitivity of 54.5%, which means that 54.5% of the diagnosis of EGFR mutations in cytology/histopathology samples with positive results could be detected by positive ctDNA examination and the specificity value of ctDNA measurements obtained in this study was 90. 0% means that 90.0% of the diagnosis of negative EGFR mutations will be excluded in ctDNA positive patients.

On examination, the NDP value was 81.8%, which means that if the ctDNA test was positive, then there was an 81.8% chance of a positive EGFR mutation diagnosis. While the NDN value is 70.6%, which means that if the ctDNA is negative, there is a 70.6% chance of diagnosing an EGFR mutation with a negative result.

The RKP value is 5.45, which means that the possibility of a patient with a positive ctDNA result will get a

diagnosis of an EGFR mutation with a positive result of 5.45 times greater than a negative ctDNA. The RKN value is 0.505, which means that the likelihood that a patient with a negative ctDNA measurement value will get a diagnosis of an EGFR mutation with a positive result is 0.505 times less than a patient with ctDNA with a positive result.

DISCUSSION

This study found a total sample of adenocarcinoma lung cancer patients who were examined for ctDNA and EGFR mutations with 73 cytology/ histopathological samples. The subjects of this study were 38 women (52.1%) who suffered from adenocarcinoma lung cancer, this is in accordance with the histological prevalence of adenocarcinoma tumors which occurred more in women over three decades, with the incidence increasing slowly.[8]

The age of the patients as the subjects in this study tend to be ≥40 years with 91.8%, where age ≥40 years was a high risk of lung cancer.[9] EGFR mutations in cytology /histopathological samples in this study occurred many deletions of exon 19, there were 18 people (24.7%) and 10 exon 21 L858R mutations (13.7%), Pal et al stated that the most common mutations were in exon 19 and exon 21 L858R2. Lyu et al's research in 2018 showed that ctDNA examination had higher accuracy against deletions of exon 19 and exon 21 L858R, in a study conducted at dr. Moewardi showed that exon 19 deletions were 16 people (21.9%) and exon 21 L858R, namely 7 people (9.6%).[10]

This study shows that 58.9% of patients do not smoke, this may be due to the number of female subjects more than men. Table 1 shows that the subjects of this study are advanced stages patients, with stage IIIC and IV with metastases in various places, Cheng et al in 2017 stated that 57% of patients in the US were diagnosed at an advanced stage and had metastasis. Qiu et al's (2015) study cited that patients with advanced stages have high levels of circulating tumor DNA, the current hypothesis indicates that the amount of ctDNA is associated with tumor volume and metastasis.[11]

The results of this study indicate that the number of cytological samples (TTNA, bronchial brushing, bronchial rinse, FNAB, pleural fluid) was higher than the histopathological samples (core biopsy, forceps biopsy). A study conducted by Yatabe in 2015 showed that 98% of the data for examining EGFR mutations in Indonesia were

cytology samples and 2% biopsy samples.[12]

Hlinkova's research in 2013 showed that 85.9% of cytological samples were used to examine EGFR mutations. Two-thirds of patients are at an advanced stage when they were diagnosed for lung cancer, only small biopsy or cytology specimens are available for EGFR examination in the majority of patients. Any type of small biopsy or cytological specimen is suitable for examination of mutations that have been confirmed by reports from various laboratories around the world.[12]

The results of EGFR mutations in cytology/histopathology samples (table 2) and the results of EGFR mutations in blood plasma samples (ctDNA) in table 3 based on sex showed that more women were 22 subjects and 17 subjects were male. These results are in accordance with the study by Zhang et al. In 2016 which concluded that mutations were more common in women (43.7%) than in men (24%). The clinic pathological features that correlate with the EGFR mutation include East Asian ethnicity, adenocarcinoma histology, women and a history of never smoking.[13]

The kappa test results in table 4 show a value of 0.459, which means the level of concordance between the ctDNA results and the examination of the EGFR mutation in the cytology/ histopathology sample is moderate, with P=0.0001 which means statistically significant with a sensitivity of 54.5%, specificity of 90%, PPR 81, 8%, NEV 70.6% (table 5). These results differ from the 2016 ASSESS study regarding the suitability level of 90%, 50% sensitivity, 80% PPR, and 91% NEV, while the 2014 IFUM study had a 95% conformance rate, 73% sensitivity, 99% specificity, 94% PPR, and 95% NEV.[14] The IGNITE Study in 2013 – 2014, mutation status concordance between 2581 matched tissue/cytology and plasma samples: 80.5% (sensitivity 46.9%, specificity 95.6%).[15]

Zhang et al's study about ctDNA assessment of EGFR mutation status in Chinese patients with advanced non-small cell lung cancer in real-world setting, in this study 35 patients had both tissue and plasma samples and the detection concordance was 68.6% (24/35).[3] Mao et al in 2013 presents the meta-analysis of diagnostic tests for EGFR mutation in blood using EGFR mutation in tumor tissues as the gold standard, the sensitivity, specificity, and concordance rate were 0.61 (95% CI 0.50–0.71), 0.90 (95% CI 0.85–0.94), and 0.79 (95% CI 0.73–0.84), respectively.[15]

This difference in the level of concordance may be due to the fact that the specimens examined are not optimal, this can occur from blood collection, specimen treatment, delivery of specimens from the collection location to the examination site, DNA purification, and gaps from knowledge.[11,14]

The results of this study indicate that ctDNA has high specifications and is an effective biomarker for detection of EGFR mutation status. These results are consistent with research conducted by Qiu et al. 2015 with the conclusion that ctDNA is an effective method for detecting EGFR mutation status in KPKBSK, based on high diagnostic accuracy and specificity, ctDNA can be the main screening test for NSCLC and ctDNA analysis methods. Standardized and validation still needs to be developed.[11]

CONCLUSION

The level of concordance between the examination of the EGFR mutation of blood plasma samples (ctDNA) and the examination of the EGFR mutation of the cytology / histopathology sample was in the moderate category (kappa test 0.459) and statistically significant, with a sensitivity value of 54.5% and a specificity of 90%.

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