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The Association Between Vitamin D Receptor Gene FokI Polymorphism and Pulmonary Tuberculosis

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Abstract

Backgrounds: There is a wide range of individual responses to mycobacterium infection. However, the reason why certain people suffers from a disease when they are infected with mycobacterium while others remain healthy is still unknown. Genetic susceptibility is thought to be one of the important explanatory factors for individuals with the risk of developing pulmonary tuberculosis (TB). FokI polymorphism was one of the genetic variations within the vitamin D receptor (VDR) gene associated with pulmonary TB. In the present study, we investigated the association between VDR gene FokI polymorphism and pulmonary TB.
Method: This is a case-control study with 65 pulmonary tuberculosis patients as cases and 65 healthy subjects as controls. The PCR-RFLP technique was used to assess the polymorphism of the vitamin D receptor gene FokI. The association of the vitamin D receptor gene FokI polymorphism with pulmonary tuberculosis was statistically analyzed.
Results: The frequency of FokI genotypes determined from pulmonary TB patients were 41,5% for FF, 44,6% for Ff and 13,8% for ff, while in healthy controls, the frequency of FF, Ff and ff were present in a percentage of; 43,1%, 44,6% and 12,3%, respectively.
Conclusion: There was no significant association between the VDR gene FokI polymorphism and pulmonary TB.
Keywords: FokI polymorphism, pulmonary TB, vitamin D receptor gene

INTRODUCTION

Tuberculosis (TB) is the second leading cause of death from infectious diseases worldwide.[1,2] The global number of pulmonary TB cases has been increasing, compared to previous years. Indonesia ranks second in the largest number of pulmonary TB cases in the world, around 10%.[1] Approximately one third of the world's population has been infected with *Mycobacterium tuberculosis* (*M. tuberculosis*), but only 10% of the infected developed into an active pulmonary TB disease. The susceptibility to the disease after the infection of mycobacterium is influenced by the agent, environmental, and genetic factors.[2,3]

In the past few years, more studies addressing the impact of VDR polymorphisms on TB susceptibility have been conducted in different populations. Polymorphisms in the VDR gene may influence VDR activity and subsequent downstream vitamin D-mediated effects.[4] Four single nucleotide polymorphisms (SNP), which are the variants of VDR, including *Apa*I, *Bsm*I, *Fok*I, and *Taq*I, are the primary focus which have a role in the risk of pulmonary TB compared to the other SNPs.[5–7]

*Fok*I polymorphism (rs2228570) is a transition polymorphism C to T (ACG to ATG) located in exon 2. *Fok*I polymorphism, described as the f allele, allows the protein translation to start from the first ATG, while the F allele starts the protein translation from the location of the second ATG.[5–8] Long vitamin D receptors, coded from the f allele forms, have more three amino acids, and 1.7 times less efficient than VDR coded by the F allele forms. Therefore, this variant may affect the individuals' susceptibility to pulmonary TB.[9–11]

Based on the above description, the researchers conducted a study to investigate the association betweeen VDR gene *Fok*I polymorphism with pulmonary TB.

METHOD

This was a case control study conducted with approval from the Research Ethics Committee of the Faculty of Medicine, University of Sumatera Utara (No: 351/TGL/KEPK FK USU-RSUP HAM/2016), that compared risk factors with disease incidence by comparing a group of people with pulmonary tuberculosis (cases) to a group of people without the disease (control). The sample data was collected at Haji Adam Malik General Hospital Medan and several other health centres in Medan, conducted from April to June 2016.

The sample size in this study was 65 people in the case group and 65 people in the control group. The inclusion criteria of case samples in this study were: new untreated pulmonary TB patients or those who had received antituberculosis treatment <7 days, with positive smear bacteria in sputum based on direct smear examination or positive GeneXpert examination results, male and female patients with pulmonary TB aged 18-65 years and agreeing to participate in the study declared in writing (informed consent). Exclusion criteria in this study, on the other hand, included having HIV, Diabetes Mellitus (DM), and other severe conditions, such as a history of renal disease or liver disease.

All subjects were given informed consent, interviewed, and peripheral blood samples were obtained. DNA isolation (Promega, USA) was performed on the blood and then it was stored at -20°C. The genotype analysis of *Fok*I polymorphism of the VDR gene was performed using Polymerase Chain Reaction Restriction Fragment Length Polymorphisms (PCR-RFLP) technique with endonuclease *Fok*I restriction enzyme (Thermo Scientific). The primary *Fok*I sequence in this study is *Forward*: 5′-AGC TGG CCC TGG CAC TGA CTC TGC TCT-3′, while the primary *Reverse*: 5′-ATG GAA ACA CCT TGC TTC TTC TCC CTC-3′. Products digested by the restriction enzymes were then visualized in a Gel Documentation System tool.

The resulting genotype depends on the patterns of digestion. The depiction of electrophoresis, if truncated, would reveal the DNA bands at 169 bp and 96 bp. Otherwise, the DNA bands would be at 265 bp. The existence of restriction area is marked with the lowercase "f", while the absence of restriction area is marked with the letter "F". Whereas FF homozygote produces 265 bp band and ff homozygote produces 169 bp and 96 bp band, Ff heterozygote occurs if there are three bands of 265 bp, 169 bp, and 96 bp.

The statistical analysis used in this research was the logistic regression test. The Hardy Weinberg Equilibrium was tested on the case group and the control group using the HWE Testing Calculator web tool, which was available online.

RESULTS

The characteristics of the case group and the control group can be seen in Table 1. Distribution of genotypes and alleles of *Fok*I polymorphism of the VDR gene can be seen in Table 2. The Ff genotype was the highest genotype in both groups, with 29 people (44.6%) in each the case group and the control group.

Table 1. Characteristic from pulmonary TB patients and healthy people

Characteristic	Case (pulmonary TB)	Control (healthy people)
Age		
18-25 years	14 (21.5%)	30 (46.2%)
26-35 years	28 (43.1%)	23 (35.4%)
36-45 years	8 (12.3%)	10 (15.4%)
46-55 years	13 (20.0%)	1 (1.5%)
55-65 years	2 (3.1%)	1 (1.5%)
Gender		
Men	47 (72.3%)	42 (64.6%)
Women	18 (27.7%)	23 (35.4%)
Total	65 (100.0%)	65 (100.0%)

Table 2. The frequency of allele and genotype VDR gene *Fok*I polymorphism

*Fok*I Polymorphism	Case (pulmonary TB)	Control (healthy people)	P	OR (95% CI)	HWE Case χ^2 (p)	HWE Control χ^2 (p)
Genotype						
FF	27 (41.5%)	28 (43.1%)	-	1	0,07 (>0.05)	0,01 (<0.05)
Ff	29 (44.6%)	29 (44.6%)	0.923	1,037 (0.496-2.169)		
ff	9 (13.8%)	8 (12.3%)	0.781	1,167 (0.393-3.467)		
Allele						
F	83 (63.8%)	85 (65.4%)	0.795	1.070 (0.643-1.779)	-	-
f	47 (36.2%)	45 (34.6%)				

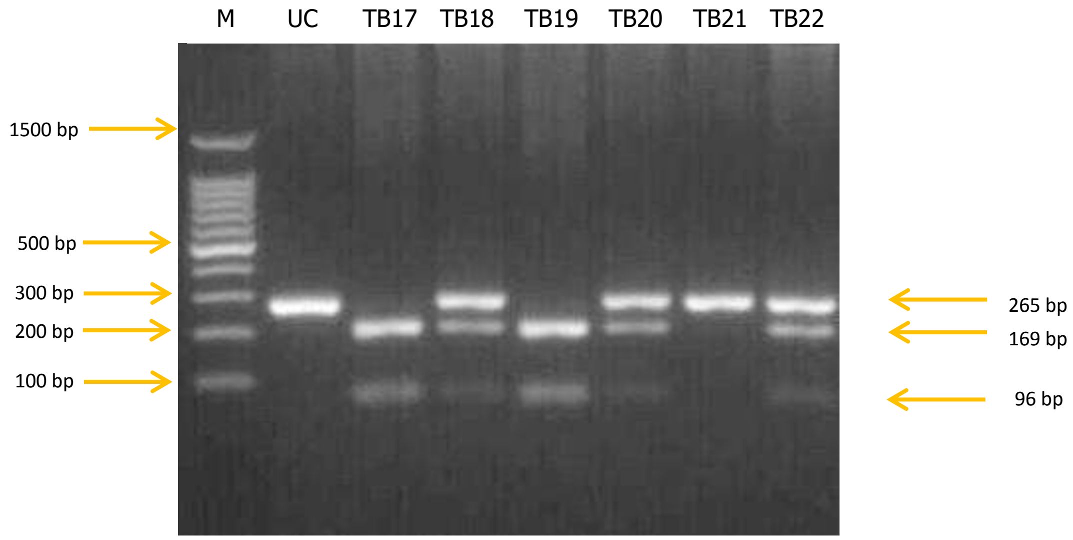

Figure 1. Image of RFLP *Fok*I polymorphism with various genotype in samples from pulmonary TB group samples. M = marker, UC = uncut. FF genotype in sample TB21 has 1 band (265 bp), ff genotype in samples TB17 and TB19 have 2 bands (169 bp and 96 bp), Ff genotype in samples TB18, TB20 and TB22 have 3 bands (265 bp, 169 bp, and 96 bp).

There was no statistically significant difference in the genotype distribution of *Fok*I polymorphism of the VDR gene between the case group and the control group (P>0.05). The frequency of the F alleles was greater than the frequency of the f alleles in both case group and control group.

The F alleles found in the case group were 83 (63.8%), whereas the f alleles found in the case group were 47 (36.2%). There was no statistically significant difference in the frequency of the F alleles and the f alleles in the *Fok*I polymorphism of the VDR gene between the case group and the control group (P>0.05). The genotype of *Fok*I polymorphism in the case group was in the Hardy-Weinberg equilibrium (P>0.05), whereas the control group was not in a state of Hardy-Weinberg equilibrium (P<0.05).[12]

The PCR product was truncated by the endonuclease *Fok*I restriction enzyme in the case group can be seen in Figure 1.

DISCUSSION

Individual reactions to mycobacterium infection vary greatly; nonetheless, the reason why some people become unwell when infected with mycobacterium while others remain healthy is unknown. Genetic susceptibility is thought to be one of the important explanatory factors for individuals with the risk of developing pulmonary TB.[13]

The VDR gene comprises of a complex of intron/exon structures, located in the long arm of chromosome 12q12-q14 and consists of 16 exons.[5] The VDR gene is known to be responsible for the genetic polymorphism affecting receptor activity and vitamin D-mediated effects.[13]

There are variations in the VDR gene polymorphisms which play a role in the susceptibility of pulmonary TB, one of which is the *Fok*I polymorphism of the VDR gene studied in this study. *Fok*I is one of the VDR variants located in exon 2.[14]

Polymorphism is a variation of DNA sequences which causes genetic diversity in the gene pool of a population. Polymorphism is formed through a mutation process which can occur due to substitution, deletion, or insertion in the order of polynucleotides. Polymorphism has a neutral effect on biological function. However, in some conditions, it may cause an impaired biological function. This happens because there is a change in the DNA sequences that encode proteins. Polymorphism can also be found in DNA areas which do not encode protein.[13]

In this study, there was no statistically significant difference in the genotype distribution of *Fok*I polymorphism of the VDR gene between the case group and the control group. This result was similar to research conducted on Peru's population.[9] Other studies in Cambodia, West Africa, and Korea suggested that there was no relationship between VDR gene polymorphism and pulmonary TB.[9,15,16]

Similarly, in the population of Kazakhs, the *Fok*I and *Apa*I polymorphisms did not have a significant relationship with the risk of pulmonary TB.[7] Studies conducted in Indonesia's population, especially Batak ethnic, showed that there was no relationship between the *Fok*I polymorphism of the VDR gene and the susceptibility of pulmonary TB.[3]

This was not in line with a study conducted on native Paraguayans which showed a link between the *Fok*I polymorphism of the VDR gene and pulmonary TB. The meta-analysis study shows that polymorphisms may have different roles in different populations. For example, there was a significant relationship between pulmonary TB and the *Fok*I polymorphism of the VDR gene in Asian population, but it was not found in African or South American population.[4,16,17]

The significant relationship between the *Fok*I and *Taq*I genotypes of the VDR gene and the susceptibility to pulmonary TB was found in Gambia and London populations.[2]

Based on a population meta-analysis study in China, the variants of homozygote VDR genes to the *Fok*I polymorphism may be more susceptible to pulmonary TB, compared to the heterozygote and wild type variants.[9]

The existence of different results from previous studies may be related to different genetic backgrounds in different populations. There are other four SNPs as variants of VDR, namely *Apa*I, *Bsm*I, *Fok*I, and *Taq*I, which play a role in the risk of pulmonary TB.[5–7]

This study only investigated the *Fok*I polymorphism of the VDR gene, while there are other SNPs variants of VDR which play a role in the risk of pulmonary TB.

CONCLUSION

There was no significant association between VDR gene *Fok*I polymorphism and pulmonary TB.

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Original Article

The Role of Incentive Spirometry On Exercise Capacity,Breathing Symptoms, Depression Rate, and Quality of Life in NSCLC Patients with Chemotherapy

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Abstract

Backgrounds: Pulmonary rehabilitation is a non-pharmacological therapy that improves breathing capacity in lung cancer patients. This study aimed to determine the effects of incentive spirometry (IS) on exercise capacity, breathing symptoms, depression rates, and quality of life in lung cancer patients with chemotherapy.
Method: This quasi-experimental study was done through purposive sampling of 32 lung cancer patients who underwent chemotherapy for at least three cycles at Dr. Moewardi General Regional Hospital, Surakarta, from December 2019 to February 2020. Experimental group performed exercise using IS for four weeks alongside their standard chemotherapy, whereas control group received only standard chemotherapy. Data on 6 minutes walking test (6-MWT) to evaluate exercise capacity, breathing symptoms (BORG scale), level of depression (HRSD questionnaire), and quality of life (SGRQ questionnaire) in both groups were collected at baseline and at the end of the fourth week.
Results: Experimental group showed higher value of 6-MWT (72.75±152.50 meters vs. 31.81 ± 27.67, P=0.010), a decrease in the BORG scale (-1.78±1.72 vs. -0.38±1.67, P=0.013), Hamilton's score improvement (-2.25±5.12 vs. -4.25±5.34, P=0.075), and improvement in the SGRQ value (-10.77±9.82 vs. -0.08±11.16, P=0.752) compared to those of control group.
Conclusion: Incentive spirometry significantly increased exercise capacity, reduced symptoms of shortness of breath lowered depression, and improved the quality of life for lung cancer patients with chemotherapy.
Keywords: 6-MWT, BORG, HRSD, SGRQ

INTRODUCTION

Lung cancer is the second leading cause of cancer. Patients with lung cancer who survived for more than five years had a 35% drop in quality of life. As many as 15% of lung cancer patients are able to adjust to chronic symptoms.[1,2]

Chemotherapy induces lung fibrosis. People with lung cancer feel dyspnea, which causes them to restrict their activity, rest more frequently, and recover slowly after strenuous activities. Chemotherapy can lead to depression and a decline in quality of life. Breathing exercises are required immediately to assist with breathing difficulties. People with lung cancer have a higher rate of psychological stress and depression, as well as a lower quality of life than people with other forms of cancer. Good breathing enable patients with lung cancer to improve their endurance and quality of life, allowing them to carry out their daily lives. The objectives of medical rehabilitation programs in non-operable lung cancer cases are to preserve and enhance patients' functional ability, lessen the severity of dyspnea, and thus minimize depression and improve quality of life.[3–5]

Incentive spirometry (IS) exercises can improve oxygen intake during inspiration, oxygen perfusion from the alveoli to the blood vessels, oxidative enzymes, myoglobin resistance to oxygen, and lung function. Increased muscle strength and pulmonary volume following inspiration will be optimized, affecting the elasticity of the pulmonary recoil, increasing the mileage of 6-MWT, improving breathing, lowering the degree of tightness, and increasing daily life activity.[6–12]

METHOD

This quasi-experimental study was done through purposive sampling of 32 non-small cell lung carcinoma (NSCLC) patients who underwent chemotherapy for at least three cycles at Dr. Moewardi General Regional Hospital, Surakarta, from December 2019 to February 2020. Samples with even numbers participated in the incentive spirometry group, while samples with odd numbers were included in control group.

NSCLC patients over the age of 40 who were non-operable, scored 70-90 in performance status, had at least three cycles of chemotherapy with platinum base regimens, were able to do incentive spirometry, and were willing to participate in the study by completing a written consent were eligible for this study. Exclusion criteria were lung cancer patients with acute infections, patients who were unable to perform the IS maneuver, patients with severe cardiac issues, patients with neurological deficits who were unable to sit upright, patients who had grade 3 vomiting side effects, and patients who experienced pleural effusion during the study.

Patients with acute infections during the trial, lost to follow up, deceased, or exhibited pleural effusion during the study meet the criteria for discontinuation. Four weeks of IS exercises were given to the experimental group alongside the standard chemotherapy, whereas subjects in the control group received only standard chemotherapy. The 6 minutes walking test (6-MWT) to evaluate exercise capacity, breathing symptoms (BORG scale), level of depression (HRSD questionnaire), and quality of life (SGRQ questionnaire) results were noted at baseline and by the end of the fourth week for all subjects.

Data of all variables were analyzed using SPSS 21 for Windows. Analysis of normally distributed data was conducted with an unaltered t-test, while abnormally distributed data was performed using Mann-Whitney. The result is considered to be statistically significant when $P<0.05$.

RESULTS

There were 36 patients recruited for this study, but two patients in the experimental group were not eligible due to their inability to perform IS techniques because of their clinical conditions and two patients in the control group passed away. The remaining 32 participants who completed the four-week trial period were divided into two groups, 16 in the experimental group and 16 in the control group.

The experimental group age averaged 56.25±12.92 years, and in the control group, an average of 63.06±9.71 years. Chemotherapy cycles in the treatment group averaged 3.81±1.05 times, and in the control group, an average of 3.56±0.96times.

Table 1. Characteristics of ResearchSubject

Characteristics	Group		P
	Experimental	Control	
Gender			
Male	12 (75.0%)	9 (56.3%)	0.246
Female	4 (25.0%)	7 (43.8%)	
Age[a]	56.25±12.92	63.06±9.71	0.102
Education[b]			
Non- School	2 (12.5%)	1 (6.3%)	0.179
Elementary	9 (56.3%)	6 (37.5%)	
JuniorHigh School	1 (6.3%)	2 (12.5%)	
Senior High School	4 (25.0%)	7 (43.8%)	
Job[c]			
Labor	3 (18.8%)	3 (18.8%)	0.193
Housewives	1 (6.3%)	4 (25.0%)	
Retirement	0 (0.0%)	3 (18.8%)	
Farmers	7 (43.8%)	3 (18.8%)	
Private	2 (12.5%)	2 (12.5%)	
Self employed	3 (18.8%)	1 (6.3%)	
Types of lungs cancer[c]			
AdenoCa	8 (50.0%)	10 (62.5%)	0.384
large cell	0 (0.0%)	1 (6.3%)	
Squomous cell	8 (50.0%)	5 (31.3%)	
Smokers[c]			
Former smokers	4 (25.0%)	8 (50.0%)	0.144
Non- smoking	12 (75.0%)	8 (50.0%)	
Drugs of chemotherapy			
Cisplatin[c]	15 (93.8%)	11 (68.8%)	0.172
Carboplatin[c]	1 (6.3%)	5 (31.3%)	0.172
Pemetrexed[c]	5 (31.3%)	3 (18.8%)	0.685
Pakliktasel[c]	2 (12.5%)	5 (31.3%)	0.394
Docetaxel[c]	4 (25.0%)	5 (31.3%)	1.000
Gemsitabine[c]	4 (25.0%)	2 (12.5%)	0.654
Navelbine[c]	1 (6.3%)	2 (12.5%)	1.000
Cycle of chemotherapy[LY717][b]	3.81±1.05	3.56±0.96	0.370

Note:[a]. Normal numerical data, Independent test samples test, t-test; b. Abnormal numerical dataor ordinal data, Mann Whitney test; [c]. nominal categorical data; frequency (%), Chi-square/Fisher exact test; the significant result if the test produces $P<0.05$.

Quantitative characteristic variables, i.e., age and chemotherapy cycles in the control group and treatment after being tested for normality data with Shapiro-Wilks tests, all showed that the age variables were normally distributed, so that homogeneity tests were conducted with pair t-test for independent samples. The homogeneity test results of variable age characteristics showed value of P=0.102, and for the chemotherapy cycle, value of P=0.370. The value of P>0.05 means the variable characteristics of the lifespan and chemotherapy cycle are homogeneous or do not differ between the treatment group and the control group.

Males were predominant in the experimental group (75.0%), contrary to the control group where females were slightly higher (56.3%). There were 9 subjects (56.3%) in the experimental group that graduates from elementary school only. High school graduates were 43.8% in the control group. Occupations in the experimental group were predominantly farmers (43.8%), whereas in the control group, occupations were evenly distributed, with the majority being housewives (25.0%).

Adenocarcinoma (50.0%) and squamous cell carcinoma (50.0%) were found to be equal in the experimental group. In comparison, Adenocarcinoma (62.5%) were the most common type of cancer cells found in the control group, with squamous cell carcinoma following after. Non-smoking subjects were predominant in the experimental group (75.0%) and equal to smoking subjects in the control group (50.0%). The most widely used therapy was Cisplatin, in both experimental (93.8%) and control group (68.8%). None of the characteristics mentioned above showed significant correlation (P>0.05) among both groups.

The 6-MWT examination of pre, post, and post-pre differences in experimental and control groups can be seen in Table 2.

Pre-test of 6-MWT in the experimental group obtained an average of 248.00±3.02, and post-test 6-MWT averaged 323.13±103.26. The difference between the 6- MWT post and pre-test obtained increased about 72.75±52.20. Pre-test 6-MWT in the control group obtained an average of 214.13±91.48, and post-test 6-MWT averaged 211.00±102.45. The difference between the 6-MWT post-pre in control group is about 31.81±27.67.

In the experimental group, the vlue of P=0.001, which means there were statistically significant changes in 6-MWT. While the control group gets value of P=0.776, which means that in the control group, there was no significant 6-MWT change. The provision of incentive spirometry treatment effectively improve 6-MWT, as evidenced in the non-paired difference test at the post-pre difference value (P=0.010).

Examination of pre, post, and differences in post-pre treatment and control groups can be seen in Table 3.

Table 2. 6-MWT Difference Test Between experimental group and control group

Group	6-MWT			
	Pre	Post	P	Post – Pre
Experimental (*Spirometri*)	248.00±83.02	323.13±103.26	0.001[c]	72.75 ±52.20
Control	214.13±91.48	211.00±102.45	0.776[d]	31.81 ±27.67
P	0.213[b]	0.004[a]		0.010[b]

Note: The observation results have described the meanof SD, [a]. test of different groups of unpaired passed normal variable data (independent t-test), [b]. test different groups of ungrouped did not pass the normal variable data (Mann Whitney), [c]. test different groups of pairs pass the normal variable data (Pair t-test), [d]. test different groups of pairs do not pass normal variable data (Wilcoxon rank test). Significant result test is indicated by $P<0.05$.

Table 3. The Difference in Shortness of Breath test between the experimental Group and the Control Group

Group	Shortness of Breath			
	Pre	Post	P	Post – Pre
Experimental (*Spirometri*)	3.25±1.88	1.47±1.12	0.004[d]	-1.78±1.72
Control	2.44±1.71	2.06±1.34	0.383[c]	-0.38±1.67
P	0.287[b]	0.184[a]		0.013[b]

Note: The results of the observations are described with the mean SD, [a]. test different groups of un-paired passed normal variable data (independent t-test) [b]. test different groups of not paired did not pass normal variable data (mann whitney), [c]. test different groups of pairspassed normal variable data (Pair t-test), [d]. testdifferent groups of pairs did not pass normal variable data (wilcoxon rank test). Significant result if the test yields $P<0.05$.

Table 4. Hamilton Score Difference Test(Depression) between the experimental group and the control group.

Group	Hamilton Score			
	Pre	Post	P	Post – Pre
Experimental (*Spirometri*)	10.75±5.25	6.50±5.55	0,006[c]	-4.25±5.34
Control	13.94±6.78	11.69±6.76	0,109[d]	-2.25±5.12
P	0,147[a]	0,038[b]		0,075[b]

Note: The results of the observations are described with mean SD, [a]. t est of different groups of ungroupspassed the normal variable data (independent t test), [b]. test different groups of ungrouped do not pass normal variable data (Mann Whitney), [c]. test different groups of pairspass normal variable data (Pair t-test), [d]. test different groups of pairs do not pass normal variable data (Wilcoxon rank test). Significant ifthe result test $P<0.05$.

Table 5. SGRQ (Quality of Life) Score Pre,Post, and Difference of Post-Pre experimental and Control Groups.

Group	SGRQ Score			
	Pre	Post	P	Post – Pre
Experimental (*Spirometri*)	39.57 ±17.41	28.80 ±13.52	0,001[c]	-10.77 ±9.82
Control	45.56 ±12.48	45.63 ±17.35	0,979[c]	0.08 ±11.16
P	0,227[a]	0,005[a]		0,002[b]

Note: The observations' results were described with the mean SD, [a] unpaired group difference test passed normal variable data (independent t- test). [b] the unpaired group difference test did notpassed normal variable data (Mann Whitney). [c]the paired group difference test passed normalvariable data (Pair t-test). [d] the paired group difference test does not normal variable data (Wilcoxon rank test), significant if the test resulted in $P<0.05$.

Hamilton's examinations of the pre, post, and post-pre differences of treatment and control groups are shown in Table 4. Based on the Shapiro Wilk test, the distribution of Hamilton's observation data on the unpaired group difference test passed the normal variable data with the independent t-test, namely the pre-test data. In contrast, the data that did not pass the normal variable data was assessed with the Mann Whitney test, namely the pre-test and post-pre test data. The pairwise difference test in the experimental group passed the normal variable data assessed with the paired t-test, while the control group that did not pass the normal variable data was calculated with the Wilcoxon rank test.

Hamilton's pre-test score in the experimental group is about 10.75±5.25, and Hamilton's post-test is about 6.50±5.55. The score in Hamilton's post and pre-test in experimental group is decreased (improvement) about 4.25±5.34. Hamilton's pre-test in control group score is about 13.94±6.78, and Hamilton's post-test score is about 11.69±6.76. Hamilton's post and pre-test scores in the control group show decrease (improvement) about -2.25±5.12.

The p-value of the experimental group is P=0.006, which means that there were significant declines in Hamilton's score. In contrast, the p-value of control group is P=0.109, which means that the control group did not have significantly decreased Hamilton's score. Subjects who were given IS show decrease in Hamilton's score better than the control group, it means that giving IS could improve depression.

SGRQ examination pre, post, and the difference in pre-post treatment and control groups can be seen in Table 5. Based on the Shapiro Wilk test, the distribution data from the SGRQ score in the unpaired group difference test which passed the normal variable data, was assessed by independent t-test. In contrast, the data that did not pass the normal variable data was assessed by Mann Whitney test. The paired difference test in the experimental group and the control group which passed the normal variable data assessed by the paired t-test.

SGRQ pre-test score in the experimental group is about 39.57±17.41 and SGRQ post-test score about 28.80±13.52. The SGRQ score in the post and pre-test in the experimental group decreased (improvement) about -10.77±9.82. SGRQ pretest score in the control group is about 45.56±12.48 and SGRQ posttest score about 45.63±17.35. The SGRQ score the pre and post-test in the control group increased (worsening) about -0.08±11.16.

The p-value in experimental group is P=0.001, which means that the experimental group significantly decrease in the SGRQ score. In contrast, the p-value in control group is P=0.979, it shows that the control group did not significantly change the SGRQ score. Subjects who were given IS show a decrease in SGRQ better than the control group. The IS effectively improved quality of life; this was evidenced in the unpaired difference test on the post-pre difference value (P=0.002).

DISCUSSION

The gender of patients in IS group was mostly male with 12 male patients (75.0%), while in control group was mostly female, with 9 female patients (56.3%). The mean age in IS group 56.25±12.92 years and around 63.06±9.71 years in the controlgroup. Type of cancer cells in the IS groupwas Adenocarcinoma and Squamous cell, each about 8 patients (50.0%), while in the control group, were mostly Adenocarcinoma. From various studies, it can be seen that lung cancer patients' characteristics are dominated by men at the age of 40 and smokers. Adenocarcinoma type remains the most common cause.

The experimental group mostly not smoke whose were 12 patients (75.0%), while thecontrol group former smokers and non-smokers had the same proportion, whose were 8 patients (50.0%). Smoking habits have a strong association with the incidence of lung cancer; females who smoke passively are at a higher risk of developing lung cancer than those who are not exposed to secondhand smoke. Approximately 80% oflung cancer deaths were estimated to be dueto smoking.[13]

Education in experimental group mostly elementary school, whose were 9 patients (56.3%), the control group mostly with high school education, whose are 7 patients (43.8%), the treatment group's occupation was primarily farmers, whose were 7 patients (43.8%), while in the control group,the patients' occupation was almost housewife, whose were 4 patients (25.0%).

Mostly chemotherapy drug was Cisplatin in both experimental and control groups. Chemotherapy cycles mean value in the experimental group was about 3.81±1.05 times and in the control group was about 3.56±0.96 times. The decrease in DLCo value was obtained by 10% after three cycles of chemotherapy; therefore, this study was conducted on patients at least three cycles of chemotherapy. Cisplatin can cause a decrease in the diffusion capacity of the alveolar-capillary membrane.[14,15]

In contrast, carboplatin can cause hypersensitivity reactions and has low pulmonary toxicity. Still, researchers have not found studies explicitly comparing the level of toxicity in the lungs between Cisplatin and carboplatin. Platinum compounds have pulmonary side effects, including interstitial lung disease, particularly cryptogenic organizing or eosinophilic pneumonia, and diffuse alveolar damage.[14,15]

Pulmonary rehabilitation is a non-pharmacological therapy aimed at improving pulmonary function, reducing respiratory complaints, and improving patients' quality of life. *Breathing exercises* are one of the most commonly used pulmonary rehabilitation exercises because they are cheap and easy to do on patients with *incentive spirometry. Incentive spirometry* increases intrapleural and intra alveolar pressures after deep inhalation and through increasing transpulmonary pressure gradients.[2,16]

Goulnar, et al in 2009 found that the 6-MWT was an easy, safe and inexpensive way to assess lung function. They found there was a decrease distance of the 6-MWT after two cycles of chemotherapy. Tarumi, et al reported an increment of lung function in the form of an increment in forced vital capacity (FVC) and forced expiratory volume in 1 minute (FEV1) in lung cancer patients with chemoradiotherapy who undergo pulmonary rehabilitation for 10 weeks. Tokarski, et al found that pulmonary rehabilitation increased oxygen partial pressure (pO2) and oxygen saturation

(SaO2) associated with increased KVP and FEV1 during first-line chemotherapy.[10]

Incentive spirometry consists of a mouthpiece and three balls which are similar with volume inspiration value which is 600 ml, 900 ml, and 1200 ml. The balls will slowly rise on maximum inspiration, then hold your breath as long as possible. Incentive spirometry practice strengthens inspiratory muscles so which will improve pulmonary function. Respiratory symptoms or shortness of breath can be reduced, cause an increment of exercise capacity, and ultimately improve the patient's quality of life.[17]

Symptoms of shortness of breath are estimated to occur in 55-87% of lung cancer patients. Pulmonary rehabilitation is needed to treat shortness of breath, exercise resistance, strength, confidence, and retrain breathing to relieve shortness of breath and improve air exchange. Pulmonary rehabilitation helps relieve chemotherapy-related symptoms to enhance tolerance and efficacy of chemotherapy drugs. Pulmonary rehabilitation programs to help reduce shortness of breath are carried out for 4-6 weeks.[10,18]

The questionnaire for shortness of breath symptoms that are often used to evaluate chronic pulmonary rehabilitation is the BORG scale. This study uses the BORG scale to assess the exercise results because this questionnaire is subjective, simple, easy, and validated.

Changes in lung volume, lung mechanics, and airway in lung cancer stimulate the stretching of receptors in the trachea and bronchi. The increase in lung volume activates mechanoreceptors in the respiratory muscles, which are thought to mediate the length-tension relationship with changes in chest wall ratio. The mechanismfor improving dyspnea due to exercise is the adaptation to peripheral muscle function leading to increased oxygen extraction and utilization, which reduces metabolic acidosis, the need for ventilation,and improves lung mechanics.[13]

The average level of depression in this study lung cancer patients had mild depression. Depression and anxiety significantly contribute to functional disability, perceptions of poor health, and poor well-being in chronic disease. Depression occurs in patients with chronic symptoms and limited airflow. Chemotherapy can reduce oxygen capacity, especially during exercise. Depression is known to cause agitation or anergia and fatigue, which add to the patient's functional limitations so that depression impacts the patient's quality of life. Research by Wei Lu, et al in 2012 showed a significant reduction in symptoms of depression and anxiety caused by shortness of breath. It decreased the ability to perform daily activities and showed an increase in the quality of life after surgery in lung cancer patients. The exercise, disease education, and psychosocial support components of a rehabilitation program may have contributed, separately or in combination, to reducing depression.[11,13,19,20]

Lung cancer patients have complaints such as shortness of breath, coughing, weakness, anxiety, depression, difficulty sleeping, and pain. This causes even though lung cancer patients experience a survival rate of more than fiveyears, there is a decrease in the quality of life in 35% of cases. Patients with respiratory disorders have skeletal muscle dysfunction, reduced exercise ability,symptoms such as dyspnea, coughing, fatigue, anxiety, depression, and impaired quality of life.[2,11,20]

They measure the quality of life using the SGRQ questionnaire, which assesses several components, namely symptoms, activity, and the impact caused by the disease.[19] Scale 0, which is the best health status, and scale 100, which is the worst health status, the average value of the SGRQ scale in this study is below 50. This study proves that lung cancer patients undergoing chemotherapy have anaverage score of not lousy health status, but not good health status.

Tiwary, et al in 1989 found improvement in symptoms of shortness of breath and clinical improvement in COPD patients using incentive spirometry in line with the progress of the patient's quality of life. Glatkii et al in 2011 reported that pulmonary rehabilitation increased CVP and FEV1 in cancer patients who underwent both surgery and chemotherapy, followed by an increase in quality of life.[13]

This research has limitation such as subjectivity in answering questionnaires, small research population, and less research time.

CONCLUSION

Based on the study results, it can be concluded that there were significant improvement between the experimental and control group on exercise capacity, symptoms of breathlessness, depression level, and quality of who underwent chemotherapy.

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CT Guided TTNA and Core Biopsy in Suspected Lung Cancer, Review of Cases in Adam Malik General Hospital, Medan

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Abstract

Backgrounds: The cytological and histopathological findings establish the type of lung cancer cells as the definitive diagnosis of lung cancer. This study aimed to determine the characteristics of lung cancer patients in terms of age, mean age, gender, staging, and the proportion of lung cancer cells by cytologic examination of Transthoracic Needle Aspiration (TTNA) and histopathologic evaluation from CT-guided core biopsy.

Method: This is a descriptive study involving 42 subjects diagnosed with lung cancer at H. Adam Malik Hospital Medan in 2016-2020 that met the inclusion criteria through consecutive sampling. Data was analysed using descriptive statistics for categorical variables.

Results: Of 42 study subjects, the 60–71-year age group had the highest percentage of lung cancer (42.9%). Male (71.4%) was higher than female, the most common lung cancer staging was IVA (57.1%), and adenocarcinoma was found to be the most frequent type of lung cancer in both cytology (33.3%) and histopathology (31.0%).

Conclusion: We concluded that core biopsy is superior in diagnosing lung cancer compared to TTNA.

Keywords: core biopsy, cytology, histopathology, TTNA

INTRODUCTION

Lung cancer, in its broadest meaning, refers to all cancers of the lungs, including malignancies that originate in the lungs and malignancies that originate outside the lungs. Lung cancer refers to primary lung cancer, which is defined as malignant tumors that arise from the bronchial epithelium, also known as bronchial carcinoma (bronchogenic carcinoma). Lung cancer is especially lethal because it has the worst prognosis, with high mortality and morbidity, a low survival rate, and difficulties in early detection and screening.[1,2]

Lung cancer was rare in the early 20th century, but it is gradually becoming more common. According to the 2012 GLOBOCAN report, there were 1.8 million new lung cancer cases globally, 12.9% of the total estimated cancer incidence in 2012. The global geographic distribution of lung cancer shows marked regional variation. Males have the highest incidence of lung cancer in Central and Eastern Europe (53.5 per 100,000) and East Asia (50.4 per 100,000). Central and western Africa show low incidence rates (2.0 and 1.7 per 100,000, respectively). Females tend to have a lower incidence rate and a slightly different geographic distribution, particularly if they have a history of smoking.[3,4]

Indonesia ranks third after China and India, with the incidence of cancer reaching 25,322 cases with a death rate of 22,522 cases. Lung cancer was estimated to affect 1,098,700 males and 491,200 females worldwide in 2012, accounting for 24% and 14% of all cancer deaths in males and females, respectively. Smoking is strongly linked to lung cancer incidence, with long-term smokers having a 10% risk, and those without a smoking history having a 10-15% risk due to environmental and genetic factors.[5–7]

Several studies have shown that the characteristics and clinical features of lung cancer patients have not changed. The data show more cases in males aged >40 years and smokers. The most common histologic finding (85%) is Non-Small Cell Lung Carcinoma (NSCLC); the results show that the 5-year survival rate of early-stage lung cancer was around 14%, and when it is in an advanced stage, only about 10% survived an average of 9-14 months.[1,8]

Histopathological analysis of lesions in the lung is mandatory if lung cancer is suspected to determine the optimal diagnostic setting. The specimen material acquired should be adequate for a definitive histopathological diagnosis and should be superior to cytology.

In some cases, particularly adenocarcinoma, molecular analysis is essential. Two methods to obtain sufficient biopsy samples are flexible bronchoscopy and CT-guided lung biopsy. Flexible bronchoscopy is the best method for locating proximal tumors; whereas, CT-guided lung biopsy is more accurate for locating peripheral tumors. CT-guided lung biopsy, if conducted safely, has a sensitivity of 90% for the diagnosis of lung cancer. Complications are less common, particularly hemoptysis and pneumothorax, which require the insertion of a chest tube.[9]

This study aimed to determine the profile of the histopathological examination of core biopsy and CT-guided TTNA in patients diagnosed with lung cancer.

METHOD

This is a descriptive study involving 42 subjects diagnosed with lung cancer at H. Adam Malik Hospital Medan in 2016-2020 that met the inclusion criteria through consecutive sampling. For categorical variables, the data in this study were examined descriptively. The outcome is presented in the form of frequency and percentage (proportion). This study has been approved by the Ethical Research Committee of the Faculty of Medicine at Universitas Sumatera Utara.

RESULTS

We collected data for four months (April 2020 to August 2020). This study involved 42 samples taken from the population according to the inclusion and exclusion criteria. The majority of the patients in this study were male (71.4%). The 60–71-year age group had the highest percentage of lung cancer (42.9%). A detailed description can be seen in Table 1.

Table 1. The characteristics of subjects (N=42)

Variables	n	%
Gender		
Male	30	71,4
Female	12	28,6
Age		
18-30 years old	2	4,8
31-40 years old	3	7,1
41-50 years old	2	4,8
51-60 years old	10	23,8
61-70 years old	18	42,5
71- 80 years old	5	11,9
81-90 years old	2	4,8
Average Age	59 years old	

Lung cancer staging in this study sample used the TNM system classification according to the International Staging System for Lung Cancer version 8 in 2017 and the most common lung cancer staging was IVA (57.1%) as seen in Table 2.

Table 2. Lung cancer staging (N=42)

Lung cancer staging	n	%
IA	1	2,4
IIB	5	11,9
IIIA	9	21,4
IIIB	2	4,8
IVA	24	57,1
IVB	1	2,4

The results of histopathological analysis of the core biopsy in this study consisted of Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). In this study, adenocarcinoma was found to be the most frequent type of lung cancer (31.0%) as seen in Table 3.

Table 3. Core biopsy histopathology (N=42)

Core biopsy histopathology	n	%
Adenocarcinoma	13	31.0
Poorly Differentiated Adenocarcinoma	3	7.1
Well Differentiated Adenocarcinoma	1	2.4
Adenosquamous cell carcinoma	1	2.4
Squamous cell carcinoma	11	26.2
Not representative	8	19.0
Atypical tissue	2	4.8
Melanoma metastases	1	2.4
Benign lesion	1	2.4
Yolk sac tumour	1	2.4

Cytological diagnosis of lung cancer is based on the 2015 World Health Organization (WHO) classification system and the International Association for the Study of Lung Cancer (IASLC). Pathologists analyzed the cytologic findings of the CT-guided TTNA using the following classifications was (C1) inadequate, (C2) benign smear/inflammatory smear, (C3) atypical, (C4) suspected malignant, (C5) malignant smear.

Four samples were considered inadequate, five samples were benign smears, four samples were hemorrhagic smears, two samples were atypical, one was suspected malignant, and 26 samples were malignant (Table 4).

Table 4. Transthoracic Needle Aspiration Cytology (N=42)

Transthoracic Needle Aspiration Cytology	n	%
C1 Inadequate	4	9.5
C2		
Benign Smear	5	11.9
Hemorrhagic smear	4	9.5
C3 Atypical	2	4.8
C4 Suspected malignant	1	2.4
C5		
Malignant smear	3	7.1
Adenocarcinoma	14	33.3
Squamous cell carcinoma	9	21,.4

DISCUSSION

In this study, we found that in establishing lung cancer diagnosis using a core biopsy, more malignant cells were found in the core biopsy (69.1%) than in the TTNA procedure (62.2%). It could be because the TTNA needle size is smaller than the Core biopsy, thus the sample adequacy of the Core biopsy is better than TTNA. The experience of the operator who performed the TTNA and core biopsy, the presence of a pathologist at the time of the TTNA and core biopsy were done, and the type of devices used during the procedure were also thought to be the reasons.[10]

In TTNA, one factor affects the diagnostic results of lung cancer adalah the interpretation of the anatomic pathologist who concludes of the obtained aspirate. Currently, there is no standard category in the cytopathological assessment of lung cancer. Other factors that affect the adequacy of samples on TTNA and Core Biopsy are the size and location of the nodules found on CT scans and the number of needle punctures in sampling. In contrast, the depth of the needle puncture and the patient's position does not affect the diagnostic value.[11,12]

Core biopsy is preferable to TTNA because it minimizes the likelihood of diagnostic failure and to obtain sufficient tissue samples for molecular histopathological analysis. TTNA, on the other hand, has advantages because it is less expensive, Rapid On-site Evaluation (ROSE) can be directly performed, and pathologists can directly assess the adequacy of samples and types of cancer cells so that an accurate diagnosis is established.[13,14]

Although Core Biopsy produces a higher diagnostic value than TTNA, Core Biopsy has more significant complications than TTNA. The most common complications found are pneumothorax and bleeding. It is associated with a larger needle size in Core Biopsy compared to TTNA. It is the reason that a core biopsy is not always necessary, simply using TTNA and accompanied by a pathologist will produce a better diagnostic value.[15]

There is a wide variation in reporting the diagnostic accuracy of TTNA wherein the sensitivity, specificity and accuracy of TTNA are 82 to 99%, 86 to 100% and 64 to 97%, respectively. Core Biopsy shows a slightly higher sensitivity, specificity, and overall accuracy, with 89%, 97% and 93%, respectively. This study recommends using needle sizes 18 and 20 and the coaxial technique to improve diagnostic results resulting in a diagnostic accuracy value of 74-95% for the diagnosis of malignancy. Schneider et al. discovered that Core Biopsy had statistically better sample size adequacy for molecular testing than TTNA (67% vs 46%; P=0.007)[16]

The study that measured the diagnostic accuracy of CT Scan-guided Core biopsy of small lung nodules was 96.1%, with 100% technical success. This study indicates that CT-guided core biopsy is an effective method for diagnosing small lung nodules. Previous studies showing TTNA to diagnose small lung nodules (20mm) showed that the diagnostic accuracy was only 64.6% to 77.2%. The size of the nodule affects the diagnostic accuracy of TTNA and core biopsies. The diagnostic failure of TTNA is influenced by the size of the lung nodules.[17]

Univariate analysis showed that the predictors of diagnostic success of Core Biopsy were tumour size >3 cm, use of coaxial needle and 2.5 mm thorax CT Scan slice thickness, use of additional imaging and Ground Glass Opacity (GGO) images and obstructive pneumonitis reduced the diagnostic value of Core Biopsy. The diagnostic accuracy of TTNA (82%) and Core Biopsy (92%), Core Biopsy is better in the adequacy of tissue samples in assessing anatomical pathologists to produce a correct diagnosis. The risk of pneumothorax and bleeding is greater in Core Biopsy due to a larger needle.[18,19]

This study included 42 samples. From all the samples, the majority gender is male, 30 patients (71.4%). Some previous studies analyzing TTNA and core biopsy with ct scan guidance showed more males (67.8%) and females (32.2%). Another study conducted in Japan also found that males (60%) were more common than females (40%).[12,20]

A study conducted at Chang Gung Hospital, Taiwan, found that there were 20 males and 23 females in group A (lesion ≤15 mm) and 86 males and 69 females in group B (lesion >15 mm). A study conducted at the Kosin University Hospital, Busan, North Korea, showed more male (196 patients) than female (104 patients). Based on 2018 Translational Lung Cancer Research (TLCR) data, new estimates of lung cancer in the United States in 2018 were 121,680 for men and 112,350 for women, for a total of 234,030, equivalent to 641 lung cancers diagnosed per day.[10,21,22]

In a study conducted at the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara in 2019, regarding the diagnosis of lung cancer using a CT-guided core biopsy, found that there were 78% more males and 10% females, this shows no difference from previous studies. In a study conducted at the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara in 2016, regarding the diagnostic accuracy of Ultrasound-guided TTNA in lung cancer, it was found that the males were mainly around 76.1% and followed by the females 23.9 %, this shows not much different from previous studies.[23,24]

Lung cancer is the second most common cancer diagnosis by gender, after prostate cancer in men and breast cancer in women. In 2018, lung cancer accounted for 14% of new cancers in men and 13% of new cancers in women in the US.[22]

According to hospital-based cancer registration data at the Dharmais Cancer Hospital, Jakarta, in 2003-2007, lung cancer was the most common malignancy in males (5.92/100,000), while in females, it was fourth (5.52/100,000). Data at Persahabatan Hospital Jakarta, in 2004-2006, showed that about 83.4% of lung cancer patients were male and 43.4% female patients, which was associated with a history of smoking. The number of lung cancer patients at H. Adam Malik Hospital in Medan increases; based on Melindawati's research (2008), the gender are primarily male, around 86.1%, and the aged over 60 years are around 40.8%.[8]

Several studies have shown that the characteristics and clinical features of lung cancer patients have not changed. The data show more cases in men aged over 40 years and smokers. In this study, the average age of the entire sample was 59 years. These results are not much different from previous similar studies. A previous study conducted at the Suleyman Demirel University, Isparta, Turkey, found a mean age of 64 years. A study conducted at the University of Maastricht, the Netherlands, from 35 samples found that the average age was 65 years, indicating that age is one of the risk factors for lung cancer.[1,25,26]

One of the factors influencing lung cancer prognosis is the stage of the disease. According to various reports, the majority of lung cancer patients are determined based on the disease's advanced stage. The most common staging in this study was stage IVA, which accounted for 57.1% of all staging. In Indonesia, lung cancer is typically diagnosed when the disease has progressed to an advanced stage. Early identification of lung cancer based on moderate symptoms occurs in people in stages II and III. A study on women who had never smoked at the H. Adam Malik General Hospital Medan found an elevated risk of lung cancer in women who had never smoked. Stage IV lung cancer was the most common.[1,27,28]

A study conducted at Dharmais Cancer Hospital Jakarta from 2008 to 2012 discovered that stage IV lung cancer was the most common, accounting for up to 26.2% of all cases. Because it frequently occurs without symptoms in the early stages, lung cancer is frequently discovered at an advanced level. The majority of lung cancer deaths are caused by metastases to distant organs. Lung cancer frequently spreads to other organs such as the brain, liver, bones, and adrenal glands.[29,30]

The histopathological analysis results from the core biopsy in this study used the Histopathological Classification of lung cancer, specifically Non-Small Cell Lung Cancer (NSCLC), adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and Small Cell Lung Cancer (SCLC), small cell carcinoma, and other types of cancer cells. In this study, the most common cell type was adenocarcinoma in 13 patients (31.0%).

Most of the literature shows that adenocarcinoma cells are the most common lung cancer malignancies. A study conducted at the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara in 2019, about the diagnosis of lung cancer using a core biopsy with the CT scan guidance, found that Squamous Cell Carcinoma cells were more in about ten patients (25%) followed by adenocarcinoma cells 11 patients (23%), this looks slightly different from the previous study. The results of a similar study at Sichuan University, Chengdu, China, showed that from 338 samples with histopathological results, namely 213 (63%), adenocarcinoma 7 (2.1%), squamous cell carcinoma 35 (10.4%), large neuroendocrine cells 6 (1.8%).), small cell carcinoma 20 (5.9%), Lymphoma 4 (1.2%), tumor metastases 39 (1.5%), undifferentiated lung carcinoma 14 (4.1%).[23,31]

This study shows that the most common type of lung cancer is adenocarcinoma. A study conducted at Adana Numune Hospital, Turkey, with a total of 65 samples, found histopathological results, specifically with adenocarcinoma malignancy cells, 11 (16.9%), epidermoid carcinoma 8 (12.3), small cell carcinoma 4 (6.2), lymphoma 2 (3.1%), pleomorphic carcinoma 1 (1.5%), metastatic 7 (10.8%), undifferentiated lung carcinoma 14 (21.6%), benign lesion 12 (18.4 %), Not representative 6 (9.2%). Another similar study conducted at Nanjing University, China, found that the most malignant cells were adenocarcinoma with 158 (50.9%) followed by squamous cell carcinoma with 34 (11%). The results in this study were also the most common type of lung cancer, adenocarcinoma, than other types of lung cancer cells.[12,32]

Cytological diagnosis of lung cancer using based on the 2015 World Health Organization (WHO) classification system and the International Association for the Study of Lung Cancer (IASLC). Anatomical Pathologists analyze the cytology of the TTNA procedure with CT scan guidance using the following classifications: (C1) inadequate, (C2) benign smear/inflammatory smear, (C3) atypical, (C4) suspected malignant, (C5) malignant smear. In this study found C1, C2, C3, C4, C5 4 (9.5%), 9 (21.4%), 2 (4.8%), 1 (2.4%), 26 (61.8%) respectively.

This study found that the most common malignant cells were adenocarcinoma in 14 patients (33.3%) and squamous cell carcinoma in 9 patients (21.4%). The literature also indicates that the most common type is adenocarcinoma. A study conducted at the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara in 2016, about the diagnostic accuracy of TTNA with chest ultrasound guidance in lung cancer, found 17 patients (37%) of adenocarcinoma cell types. Followed by Squamous Cell Carcinoma in five patients (10 %), this does not appear to be much different from previous studies.[24]

A similar study conducted at the Massachusetts Hospital, Boston, United States, found that there were 76 patients (88.3%) adenocarcinoma cells (88.3%), two patients (2.3%) poorly differentiated adenocarcinoma, one patient (1.16 %) pancreatic cancer metastases, benign lesion one patient (2.3%), inadequate 11 patients (12.7%). A similar study conducted at the University of Texas, United States, also found that the most adenocarcinoma cells were found in 40 patients (18.6%), squamous cell carcinomas 25 patients (11.6%), carcinoma metastases 26 patients (12%), melanoma metastases two patients (0.93%), benign lesions were 70 patients (32.5%), atypical was 13 patients (6%).[15,33]

Adenocarcinoma is the most common cell type in peripheral lesions with central fibrosis and pleural thickening, found in most smokers and nonsmokers. Adenocarcinoma is the most common type of lung cancer; about 40% of lung cancers and 60% of lung cancers and 60% of lung cancers are non-small cell carcinomas, and more than 70% of cases of routine surgery. The second most common type of cancer cells found in squamous cell carcinoma, usually found in central lesions found in smokers up to 90% with significant growth in the intraluminal part of the bronchi, causing atelectasis or obstructive pneumonia.[34,35]

The drawback of this study is that it was conducted retrospectively, which means that misinformation (bias) could have been obtained. The final diagnosis was based primarily on the pathologists' experience, which yielded disparate outcomes. Because the data from the sample was insufficient, there were limitations in the research variables in this study.

CONCLUSION

On the study subjects 42 patients, there are results in the form of the highest percentage of age 60-71 years (42.9 %), the average age is 59 years, the most gender is male (71.4%), the most lung cancer staging is IV A (57 .1 %), the most common lung cancer cell types were adenocarcinoma in cytology (33.3%) and histopathology (31,0%). We concluded that Core Biopsy is more effective than TTNA in diagnosing lung cancer.

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Cholesterol Level in Covid-19 Patients Related to Severity and Mortality: A Case Series and Literature Review

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Abstract

Coronavirus Disease 2019 (COVID-19) is a communicable disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). December 2019 in Wuhan, China, is the time and place where the first pneumonia case which SARS-CoV-2 causes was found, and WHO designated COVID-19 as a pandemic by March 2020. There are reported cases of dyslipidemia associated with SARS patients, albeit rare. Several case reports showed lower cholesterol levels compared to healthy subjects. Therefore, some argued that dyslipidemia could occur in COVID-19. Several studies have revealed that hypolipidemia is positively correlated with the severity of COVID-19. In Ulin Regional Hospital Banjarmasin, several cases found higher cholesterol levels in asymptomatic and mild-moderate COVID—19 survivor compared to patients with severe/critical COVID-19and non-survivor. Two patients in the non-survivor group showed a significant decrease in cholesterol level compared to baseline, and five patients had <150 mg/dL cholesterol level during the examination. Four mild-moderate COVID-19 survivors had cholesterol levels that were greater than 150 mg/dL at the first examination and did not decrease during the evaluation. Cholesterol is thought to play an important role in the pathological development of COVID-19, and it is associated with severity and mortality, which requires further studies.

Keywords: cholesterol, COVID-19, severity, mortality

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] SARS-CoV-2 is a new type of Coronavirus that has never been identified previously in humans. At least two Coronavirus strains have been linked to severe symptoms, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). COVID-19 patients can be asymptomatic or symptomatic, with symptoms ranging from mild to severe to critical. Acute respiratory disease syndromes, such as fever, cough, and shortness of breath, are common signs and symptoms of COVID-19. The average incubation period is 5-9 days, with the longest incubation time being 14 days.[2]

Severe cases of COVID-19 may cause pneumonia, acute respiratory syndrome, septic shock, multiple organ dysfunction/failure, and even mortality.[3] This disease started with the emergence of pneumonia cases of unknown etiology in Wuhan, China, at the end of December 2019. On Mar 11, 2020, WHO stated that COVID-19 is a pandemic.[4,5]

Coronavirus is a single-strain positive RNA virus that is encapsulated and not segmented. There are four structures of the main protein in Coronavirus; they are protein N (nucleocapsid), glycoprotein M (membrane), glycoprotein spike S (S spike), protein E (envelope). Coronavirus belongs to the order *Nidovirales*, family *Coronaviridae*.[1,6]

This Coronavirus may cause diseases to animals or humans. There are four genera: alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. Before the presence of COVID-19, there are 6 types of coronavirus that can infect human, they are HCoV-229E (alpha coronavirus), HCoV-OC43 (beta coronavirus), HCoVNL63 (alpha coronavirus), HCoV-HKU1 (beta coronavirus), SARS-CoV (beta coronavirus), and MERS-CoV (beta coronavirus.[1,6]

The Coronavirus that becomes the etiology of COVID-19 belongs to the genus beta coronavirus. Generally, it has a round shape with a pleomorphic diameter of 60-140nm. The result of the phylogenetic analysis shows that this virus is included in a similar subgenus with the coronavirus that causes the SARS epidemic in 2002-2004, Sarbecovirus. 79% RNA sequence is similar to SARS-COV, and 50% resembles MERS-COV. Based on this data, the International Committee on Taxonomy of Viruses (ICTV) names the cause of COVID-19 as SARS-CoV-2.[1,7,8]

Dyslipidemia that is associated with SARS patients has been reported, although it rarely occurs. Some case reports show lower cholesterol levels when it is being compared to healthy subjects.[9] Other studies reported a lipid metabolism disorder in SARS patients who had been recovered after 12 years of infection.[10]

Based on this study, it is presumed that dyslipidemia may occur in patients with COVID-19. Doctors and researchers, on the other hand, haven't paid much attention to this problem yet. A study reported dyslipidemia in COVID-19 patients, and it demonstrated the relationship between lower cholesterol levels and severity and mortality.[11]

Cases of hypolipidemia show a positive correlation to the severity level of COVID-19.[9] This case study will describe the cholesterol levels of 21 COVID-19 patients in relation to their severity and survival.

CASE ILLUSTRATIONS

Ulin Regional Hospital Banjarmasin has treated COVID-19 patients since Mar 14, 2020, and up to Aug 8, 2020, the hospital has treated 442 confirmed COVID-19 patients. There are various severities of

COVID-19 in which they are treated with different laboratory characteristics according to the severity level. There is a phenomenon in confirmed COVID-19 patients without symptoms/mild-moderate symptoms with higher lipid profile levels compared to COVID-19 patients with severe/critical symptoms and non-survival. Below are the descriptions of some cases.

Case 1

A woman, 29 years old, full-term pregnant with mild COVID-19, was referred to Ulin Regional Hospital, Banjarmasin for a cesarean section surgery. The patient complained of fever and cough. Body mass index (BMI) was 23.2 kg/m^2, and blood pressure was 113/92 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit.

Result from laboratory test was random blood sugar (RBS) 89 mg/dl, neutrophil-lymphocyte ratio (NLR) 4.02%, absolute lymphocyte count (ALC) 1200/ul, C-reactive protein (CRP) <6 mg/L, lactate dehydrogenase (LDH) 455 U/L, Ferritin 271 ng/mL, D-dimer 1.16 mg/L, aspartate aminotransferase (AST) 41 U/L, alanine aminotransferase (ALT) 26 U/L, Cholesterol 281 mg/dL, Triglyceride 218 mg/dL, low density lipoprotein (LDL) 215 mg/dL, and high density lipoprotein (HDL) 49 mg/dL The patient recovered after 43 days of hospitalization.

Case 2

A woman, 30 years old, full-term pregnant with asymptomatic COVID-19, was referred to Ulin General Hospital, Banjarmasin, for a cesarean section surgery. BMI was 28.9 kg/m^2, and blood pressure was 120/80 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Result from laboratory test was RBS 107 mg/dl, NLR 2.6%, ALC 2650/ul, CRP 9.2 mg/L, LDH 184 U/L, Ferritin 39.28 ng/mL, D-dimer 0.46 mg/L, AST 15 U/L, ALT 13 U/L, Cholesterol 225 mg/dL, Triglyceride 218 mg/dL, LDL 172 mg/dL, and HDL 47 mg/dL. The patient recovered after 38 days of hospitalization.

Case 3

A woman, 36 years old, full-term pregnant with moderate COVID-19, was referred to Ulin Regional Hospital, Banjarmasin, for a cesarean section surgery. Coughing was reported by the patient.BMI was 28.3 kg/m^2, and blood pressure was 130/80 mmHg. Rhonchi were heard in the right lower lobe during auscultation. Chest x-rays showed basal right pulmonary infiltrate. Result from laboratory test was RBS 93 mg/dl, NLR 2.25%, ALC 2360/ul, CRP 31.4 mg/L, LDH 507 U/L, Ferritin 370.83 ng/mL, D-dimer 5.08 mg/L, AST 14 U/L, ALT 10 U/L, Cholesterol 274 mg/dL, Triglyceride 214 mg/dL, LDL 218 mg/dL, and HDL 40 mg/dL. The patient recovered after 32 days of hospitalization.

Case 4

A woman, 27 years old, full-term pregnant with asymptomatic COVID-19, was referred to Ulin Regional Hospital

Banjarmasin for a cesarean section surgery. BMI was 27.8 kg/m^{2}, and blood pressure was 100/75 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Laboratory test result was RBS 79 mg/dl, NLR 3.13%, ALC 2600/ul, CRP 22.1 mg/L, LDH 242 U/L, Ferritin 29.85 ng/mL, D-dimer 6.74 mg/L, AST 12 U/L, ALT 11 U/L, Cholesterol 236 mg/dL, Triglyceride 165 mg/dL, LDL 187 mg/dL, and HDL 43 mg/dL. The patient was sent to a halfway house in stable condition after being treated for 18 days.

Case 5

A 22-year-old female with full-term pregnancy and asymptomatic COVID-19 was referred to Ulin Regional Hospital Banjarmasin for cesarean section surgery. BMI was 21 kg/m^{2}, and blood pressure was 110/70 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Laboratory test result was RBS 116 mg/dl, NLR 3.16%, ALC 1657/ul, CRP 4.2 mg/L, LDH 181 U/L, Ferritin 22.20 ng/mL, D-dimer 6.63 mg/L, AST 25 U/L, ALT 11 U/L, Cholesterol 263 mg/dL, Triglyceride 114 mg/dL, LDL 244 mg/dL, and HDL 38 mg/dL. The patient was declared cured after 27 days of treatment.

Case 6

A 54-year-old female with severe COVID-19, Chronic Kidney Disease (CKD) on regular dialysis, hypertension, and type 2 diabetes deteriorated on the 32nd day of treatment. Shortness of breath, cough, and fever were among the symptoms reported upon admission to the hospital. BMI was 24 kg/m^{2}, and blood pressure was 169/90 mmHg. There were bilateral basal rhonchi in physical lung examination. Basal right pulmonary infiltrates and cardiomegaly were shown on the chest radiograph.

Result of laboratory test was RBS 211 mg/dL, NLR 37.5%, ALC 605/ul, CRP 35.1 mg/L, LDH 885 U/L, Ferritin 2433.72 ng/mL, D-dimer 4.86 mg/L, AST 14 U/L, ALT 6 U/L, Cholesterol 191 mg/dL, Triglyceride 194 mg/dL, LDL 127 mg/dL, and HDL 25 mg/dL. The patient's lipid profile was examined again two weeks later, and a significant decrease was found. Cholesterol 73 mg/dL, Triglyceride 62 mg/dL, LDL 35 mg/dL, and HDL 16 mg/dL. The patient passed away after 34 days of treatment.

Case 7

A 42-year-old male with critical COVID-19, CKD on dialysis, heart failure, and hypertension. Shortness of breath, fever, cough, and nausea-vomitus were all mentioned by the patient. BMI was 22.91 kg/m^{2}, and blood pressure was 160/106 mmHg. There were rhonchi in all fields of the lungs during auscultation. Chest radiograph showed bilateral infiltrates on all lobes and cardiomegaly.

Result of laboratory test was RBS 138 mg/dL, NLR 39.8%, ALC 319.2/ul, CRP 78.8 mg/L, LDH 1356 U/L, Ferritin >2000 ng/mL, D-dimer 5.56 mg/L, AST 59 U/L, ALT 14 U/L, Cholesterol 126 mg/dL, Triglyceride 94 mg/dL, LDL 80 mg/dL, and HDL 30 mg/dL. After nine days, the lipid profile was reevaluated and found, Cholesterol 90 mg/dL, Triglyceride 186 mg/dL, LDL 35 mg/dL, and HDL 9 mg/dL. The patient passed away after 14 days of treatment.

Case 8

A 58-year-old male with critical COVID-19, hypertension, and type 2 diabetes complained of shortness of breath, fever, cough, and sore throat.BMI was 25.3 kg/m^2, and blood pressure was 123/79 mmHg. Rhonchi were audible on both lungs during auscultation. Chest radiograph showed bilateral infiltrates on all lobes. Laboratory test result was RBS 416 mg/dL, NLR 23.3%, ALC 630/ul, CRP 278 mg/L, LDH 1446 U/L, Ferritin 4470.10 ng/mL, no data of D-dimer, AST 74 U/L, ALT 98 U/L, Cholesterol 145 mg/dL, Triglyceride 195 mg/dL, LDL 94 mg/dL, and HDL 19 mg/dL. The patient passed away after four days of treatment.

Case 9

An overweight, 47-year-old male with critical COVID-19 complained shortness of breath, cough, sore throat, and nausea upon hospital admission. BMI was 28.9 kg/m^2, and blood pressure was 123/71 mmHg. There were rhonchi in the right lung medial basal and left lung basal in physical lung examination. The chest x-ray showed infiltrates in all right lobes and middle-lower left lobes. Result of laboratory test was RBS 88 mg/dL, NLR 6.14%, ALC 1830/ul, CRP 194.6 mg/L, LDH 1056 U/L, Ferritin >2000 ng/mL, D-dimer 0.91 mg/L, AST 108 U/L, ALT 58 U/L, Cholesterol 136 mg/dL, Triglyceride 178 mg/dL, LDL 104 mg/dL, and HDL 20 mg/dL. The patient passed away after five days of treatment.

Case 10

A 68-year-old male with hypertension and type 2 diabetes was diagnosed with critical COVID-19. Shortness of breath, fever, cough, and nausea were noted upon admission. BMI was 23.4 kg/m^2, and blood pressure was 139/90 mmHg. There were rhonchi in both middle-lower lobes in physical lung examination. There were bilateral peripheral infiltrates on chest radiograph. Laboratory test result was RBS 166 mg/dL, NLR 11.1%, ALC 751/ul, CRP 200.8 mg/L, LDH 591 U/L, Ferritin 555.63 ng/mL, no data of D-dimer, AST 50 U/L, ALT 35 U/L, Cholesterol 138 mg/dL, Triglyceride 168 mg/dL, LDL 83 mg/dL, and HDL 21 mg/dL. The patient passed away after three days of treatment.

Case 11

A 65-year-old woman with moderate COVID-19. The patient had hypertension, heart failure, and was overweight. She had a fever and a cough. During the course of treatment, the patient's condition deteriorated. BMI was 27.1 kg/m^2, and blood pressure was 130/81 mmHg. There were no rhonchi in the initial lung examination, but rhonchi were found in both lung fields during treatment. There was no infiltrate on the initial chest x-ray, but on chest x-ray evaluation, there were bilateral peripheral infiltrates.

Result of laboratory test was RBS 99 mg/dL, NLR 1.7%, ALC 1782/ul, CRP 32 mg/L, LDH 528 U/L, Ferritin >2000 ng/mL, D-dimer 1.23 mg/L, AST 139 U/L, ALT 87 U/L, Cholesterol 112 mg/dL, Triglyceride 148 mg/dL, LDL 74 mg/dL, and HDL 25 mg/dL. Six days later, laboratory evaluation was conducted, and the result was NLR 5.63%, ALC 1250/ul, CRP 229.9 mg/L, LDH 944 U/L, Ferritin 5505.42 ng/mL, D-dimer 5.10 mg/L, AST 129 U/L, ALT 115 U/L, Cholesterol 139 mg/dL, Triglyceride 180 mg/dL, LDL 67 mg/dL, and HDL 26 mg/dL. The patient passed away after 14 days of treatment.

Case 12

A 53-year-old male with a history of spondylitis TB was admitted to the hospital with diarrhea, nausea, and vomit. He was diagnosed with mild-COVID-19. BMI was 18.7 kg/m^2, and blood pressure was 105/88 mmHg. There was no abnormality from the physical lung examination. Chest x-ray was within normal limit.

Result of laboratory test was RBS 178 mg/dL, NLR 6.68%, ALC 1218/ul, CRP 38.6 mg/L, LDH 604 U/L, Ferritin 1969.52 ng/mL, D-dimer 2.48 mg/L, AST 20 U/L, ALT 44 U/L, Cholesterol 189 mg/dL, Triglyceride 171 mg/dL, LDL 158 mg/dL, and HDL 23 mg/dL. Laboratory evaluation was done two weeks later, and the result was NLR 3.94%, ALC 1070/ul, CRP 8 mg/L, LDH 144 U/L, Ferritin 804.64 ng/mL, D-dimer 0.96 mg/L, AST 12 U/L, ALT 14 U/L, Cholesterol 173 mg/dL, Triglyceride 218 mg/dL, LDL 143 mg/dL, and HDL 26 mg/dL. The patient was discharged after 20 days of hospitalization.

Case 13

An overweight, 33-year-old male was diagnosed with critical COVID-19.He complained of shortness of breath, fever, cough, and nausea. BMI was 28.7 kg/m^2, and blood pressure was 112/80 mmHg. There were rhonchi at the base of both lungs from auscultation. Chest CT showed peripheral opacity glass ground with consolidation >3cm multifocal in the right and left superior-inferior lobes.

Result from laboratory test was RBS 118 mg/dL, NLR 10.5%, ALC 448/ul, CRP 171.6 mg/L, LDH 397 U/L, Ferritin >2000 ng/mL, D-dimer 1.77 mg/L, AST 51 U/L, ALT 50 U/L, Cholesterol 146 mg/dL, Triglyceride 81 mg/dL, LDL 115 mg/dL, and HDL 34 mg/dL. Two weeks later, laboratory evaluation was conducted, and the result was NLR 3.57%, ALC 1000/ul, CRP 6.1 mg/L, LDH 251 U/L, Ferritin 1126.41 ng/mL, D-dimer 1.19 mg/L, AST 92 U/L, ALT 216 U/L, Cholesterol 162 mg/dL, Triglyceride 91 mg/dL, LDL 136 mg/dL, and HDL 37 mg/dL. The patient was treated for 23 days, and was discharged for self-isolation.

Case 14

A 60-year-old male smoker with hypertension and pulmonary TB was admitted for critical COVID-19.He complained of shortness of breath, fever, and cough. BMI was 20.8 kg/m^2, and blood pressure was 141/100 mmHg. There were rhonchi in the right middle-lower lobes and all left lobes from the physical lung examination. The chest x-ray showed infiltrates in both lungs, predominantly left.

Result of laboratory test was RBS 112 mg/dL, NLR 8.5%, ALC 1330/ul, CRP 218.6 mg/L, LDH 1250 U/L, Ferritin 2568.08 ng/mL, D-dimer 5.40 mg/L, AST 207 U/L, ALT 181 U/L, Cholesterol 236 mg/dL, Triglyceride 105 mg/dL, LDL 233 mg/dL, and HDL 30 mg/dL. Three weeks later laboratory evaluation was conducted, and the result was NLR 24.67%, ALC 520/ul, CRP 78.8 mg/L, LDH 246 U/L, Ferritin 3359.02 ng/mL, D-dimer 4.83 mg/L, AST 45 U/L, ALT 93 U/L, Cholesterol 164 mg/dL, Triglyceride 112 mg/dL, LDL 133 mg/dL, and HDL 39 mg/dL. The patient was discharged after 57 days of treatment.

Case 15

A 60-year-old male with history of stroke, hypertension, and CKD was taken to the hospital after an episode of seizure, shortness of breath, fever, cough, nausea, and vomit. He was diagnosed with moderate COVID-19. BMI was 25.6 kg/m^2, and blood pressure was 157/89 mmHg. No abnormality were found in the lung examination. The chest radiograph showed minimal infiltrates at the base of the right lung.

Laboratory result showed that RBS was 111 mg/dL, NLR 14.3%, ALC 1090/ul, CRP 357 mg/L, LDH 317 U/L, Ferritin >2000 ng/mL, D-dimer 5.16 mg/L, AST 37 U/L, ALT 9 U/L, Cholesterol 96 mg/dL, Triglyceride 77 mg/dL, LDL 72 mg/dL, and HDL 16 mg/dL. Blood work reevaluation result were NLR 1.98%, ALC 1420/ul, CRP 253.7 mg/L, LDH 144 U/L, Ferritin 2834.89 ng/mL, D-dimer 2.76 mg/L, AST 17 U/L, ALT 9 U/L, Cholesterol 180 mg/dL, Triglyceride 109 mg/dL, LDL 162 mg/dL, and HDL 26 mg/dL. The patient was discharged after 47 days of treatment.

Case 16

A 47-year-old female with hypertension and CKD came with shortness of breath and cough, and was diagnosed with moderate COVID-19. BMI was 22.9 kg/m^2, and blood pressure was 161/100 mmHg. From auscultation, there were rhonchi in both middle-lower lobes. The chest x-ray showed bilateral infiltrates in both middle-lower lobes.

Result of laboratory test was RBS 88 mg/dL, NLR 11.19%, ALC 660/ul, CRP 32 mg/L, LDH 395 U/L, Ferritin 2128,73 ng/mL, D-dimer 5.8 mg/L, AST 25 U/L, ALT 34 U/L, Cholesterol 162 mg/dL, Triglyceride 88 mg/dL, LDL 112 mg/dL, and HDL 39 mg/dL. Laboratory evaluation was conducted five weeks later, and the result was NLR 36.48%, ALC 560/ul, CRP 4.7 mg/L, LDH 306 U/L, Ferritin 4889.89 ng/mL, D-dimer 4.83 mg/L, AST 13 U/L, ALT 31 U/L, Cholesterol 174 mg/dL, Triglyceride 189 mg/dL, LDL 85 mg/dL, and HDL 51 mg/dL. The patient was discharged after 37 days of hospitalization.

Case 17

A 58-year-old female with a history of acute lymphoblastic leukemia (ALL) type L1 and hypertension came with shortness of breath, cough, and sore throat, and was diagnosed with moderate COVID-19. BMI was 18.1 kg/m^2, and blood pressure was 158/100 mmHg. Rhonchi at the base of the right lung was heard during auscultation. The chest x-ray showed infiltrates in both lung bases.

Result of laboratory test was RBS 145 mg/dL, NLR 5.59%, ALC 240/ul, CRP 116.5 mg/L, LDH 810 U/L, Ferritin 2910.37 ng/mL, D-dimer 4.85 mg/L, AST 16 U/L, ALT 32 U/L, Cholesterol 234 mg/dL, Triglyceride 132 mg/dL, LDL 141 mg/dL, and HDL 37 mg/dL. Four weeks later there was laboratory evaluation, and the result was NLR 3.66%, ALC 4192.5/ul, CRP 15.7 mg/L, LDH 254 U/L, Ferritin 2111.74 ng/mL, D-dimer 3.89 mg/L, AST 18 U/L, ALT 10 U/L, Cholesterol 167 mg/dL, Triglyceride 169 mg/dL, LDL 124 mg/dL, and HDL 33 mg/dL Patient was discharged after 37 days of treatment.

Case 18

A 51-year-old female with a history of CKD and hypertension complained of shortness of breath and cough. She was diagnosed with moderate COVID-19. BMI was 19.9 kg/m^2, and blood pressure was 169/72 mmHg. Rhonchi were audible at the base of the lungs and chest radiograph showed infiltrates in the right middle-lower lobes and cardiomegaly. R

esult of laboratory test was RBS 96 mg/dL, NLR 8.6%, ALC 1020/ul, CRP 3 mg/L, LDH 1200 U/L, Ferritin 1215 ng/mL, no data of D-dimer, AST 112 U/L, ALT 66 U/L, Cholesterol 239 mg/dL, Triglyceride 411 mg/dL, LDL 142 mg/dL, and HDL 29 mg/dL. Two weeks later laboratory evaluation was reevaluated, and the results were NLR 1.74%, ALC 930/ul, CRP 0.6 mg/L, LDH 260 U/L, Ferritin 514.0 ng/mL, no data of D-dimer, AST 20 U/L, ALT 11 U/L, Cholesterol 177 mg/dL, Triglyceride 148 mg/dL, LDL 127 mg/dL, and HDL 39 mg/dL. The patient was discharged after 22 days of treatment.

Case 19

A 61-year-old female with previous history of type 2 diabetes, hypertension, and heart failure complained of shortness of breath and was diagnosed with severe COVID-19. BMI 25.8 kg/m^2 and blood pressure was 153/99 mmHg. Rhonchi was audible on auscultation especially in the right middle-lower lobes and left lower lobes. Infiltrates were prominent on the right middle-lower lobes and cardiomegaly was visible on chest radiograph.

Result of laboratory test was RBS 272 mg/dL, NLR 15.22%, ALC 900/ul, CRP 6.0 mg/L, LDH 490 U/L, Ferritin 295.71 ng/mL, D-dimer 5.50 mg/L, AST 29 U/L, ALT 25 U/L, Cholesterol 243 mg/dL, Triglyceride 132 mg/dL, LDL 172 mg/dL, and HDL 68 mg/dL. Laboratory evaluation was conducted two weeks later and the result was NLR 2.85%, ALC 1857/ul, CRP 54.4 mg/L, LDH 239 U/L, Ferritin 569.54 ng/mL, D-dimer 1.66 mg/L, AST 29 U/L, ALT 35 U/L, Cholesterol 186 mg/dL, Triglyceride 107 mg/dL, LDL 121 mg/dL, and HDL 67 mg/dL. The patient was discharged after 18 days of treatment.

Case 20

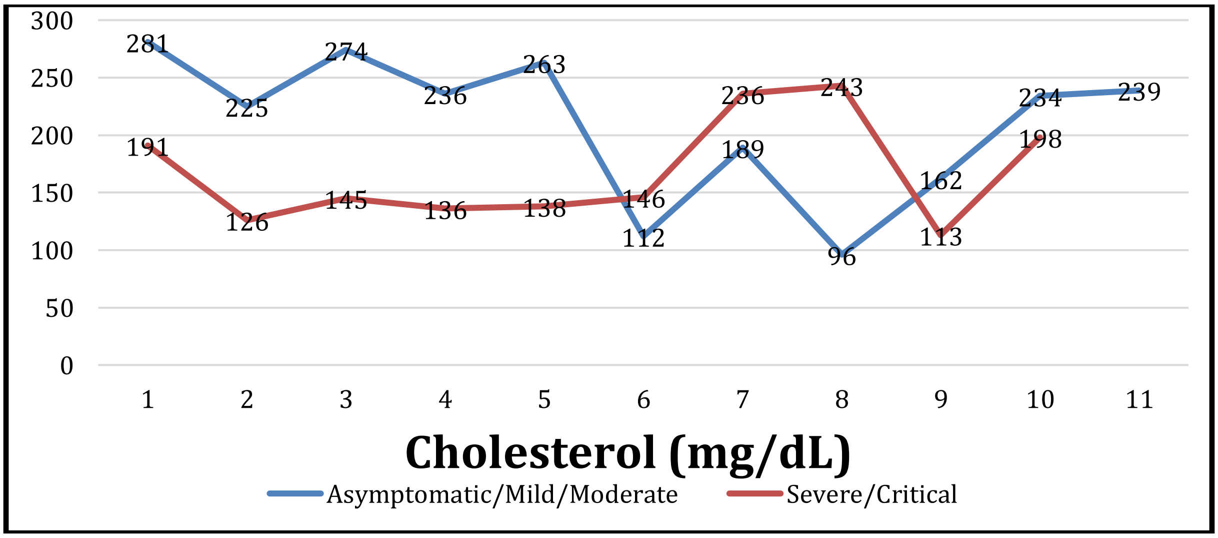
A 71-year-old male came with shortness of breath, fever, cough, diarrhea, nausea and vomit, and was diagnosed with severe COVID-19. BMI was 23.4 kg/m^2, and blood pressure was 138/65 mmHg. Rhonchi in bilateral medial basal was found from auscultation. Chest x-ray showed infiltrates in both lungs.

Laboratory examination showed that RBS 87 mg/dL, NLR 8.7%, ALC 646/ul, CRP 207.2 mg/L, LDH 852 U/L, Ferritin 446.88 ng/mL, D-dimer 4.56 mg/L, AST 63 U/L, ALT 34 U/L, Cholesterol 113 mg/dL, Triglyceride 85 mg/dL, LDL 96 mg/dL, and HDL 17 mg/dL. Four weeks later there was laboratory evaluation, and the result was NLR 3.80%, ALC 1120/ul, CRP 6.0 mg/L, LDH 213 U/L, Ferritin 208.11 ng/mL, D-dimer 0.70 mg/L, AST 27 U/L, ALT 29 U/L, Cholesterol 156 mg/dL, Triglyceride 124 mg/dL, LDL 96 mg/dL, and HDL 17 mg/dL. After 43 days of treatment, the patient was discharged.

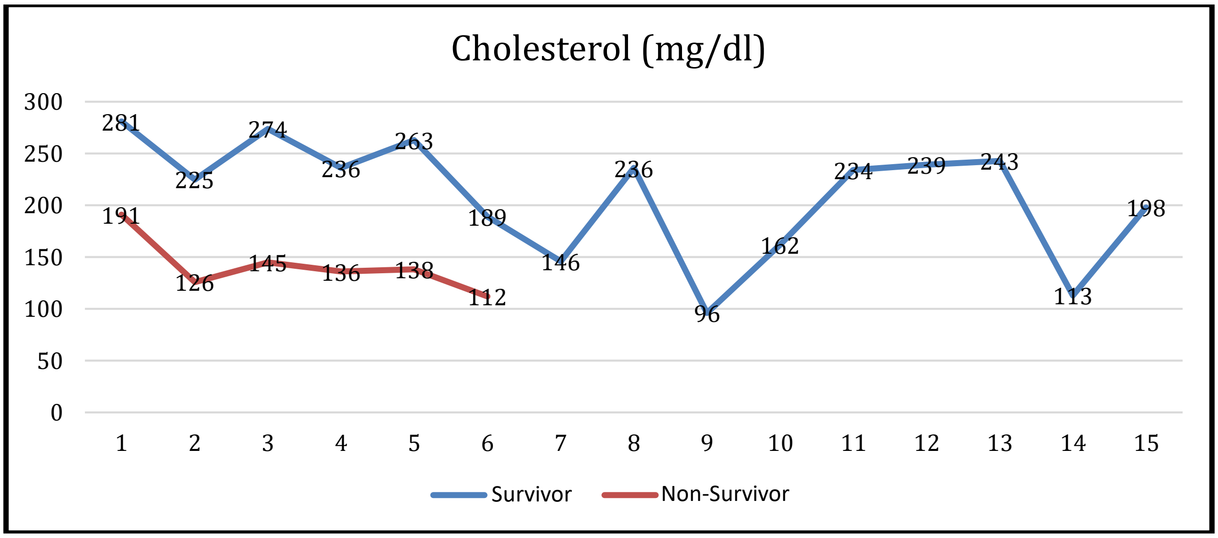
Case 21

A 58-year-old male with a history of hypertension was admitted with critical COVID-19. The patient complained of shortness of breath, fever, cough, diarrhea, epigastric pain, nausea, and vomit. BMI was 27.9 kg/m^2, and blood pressure was 149/100 mmHg. Rhonchi were audible especially in both middle-lower lobes.

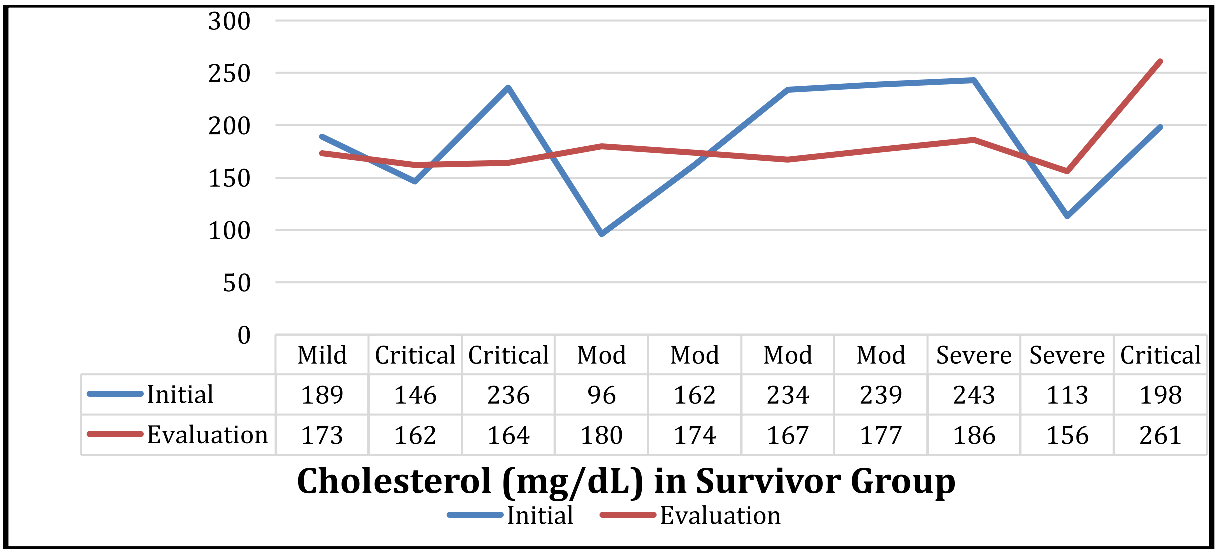
Results of chest x-ray showed infiltrates in both lungs. Result of laboratory test was RBS 140 mg/dL, NLR 6.56%, ALC 960/ul, CRP 59.8 mg/L, LDH 880 U/L, Ferritin 5835.82 ng/mL, D-dimer 1.92 mg/L, AST 92 U/L, ALT 91 U/L, Cholesterol 198 mg/dL, Triglyceride 193 mg/dL, LDL 112 mg/dL, and HDL 47 mg/dL. Laboratory evaluation was conducted four weeks later, and the result was NLR 2.0%, ALC 1725/ul, CRP <0.2 mg/L, LDH 239 U/L, Ferritin 1272.6 ng/mL, D-dimer 0.44 mg/L, AST 49 U/L, ALT 101 U/L, Cholesterol 261 mg/dL, Triglyceride 372 mg/dL, LDL 171 mg/dL, and HDL 44 mg/dL. The patient was discharged after 33 days of hospitalization.



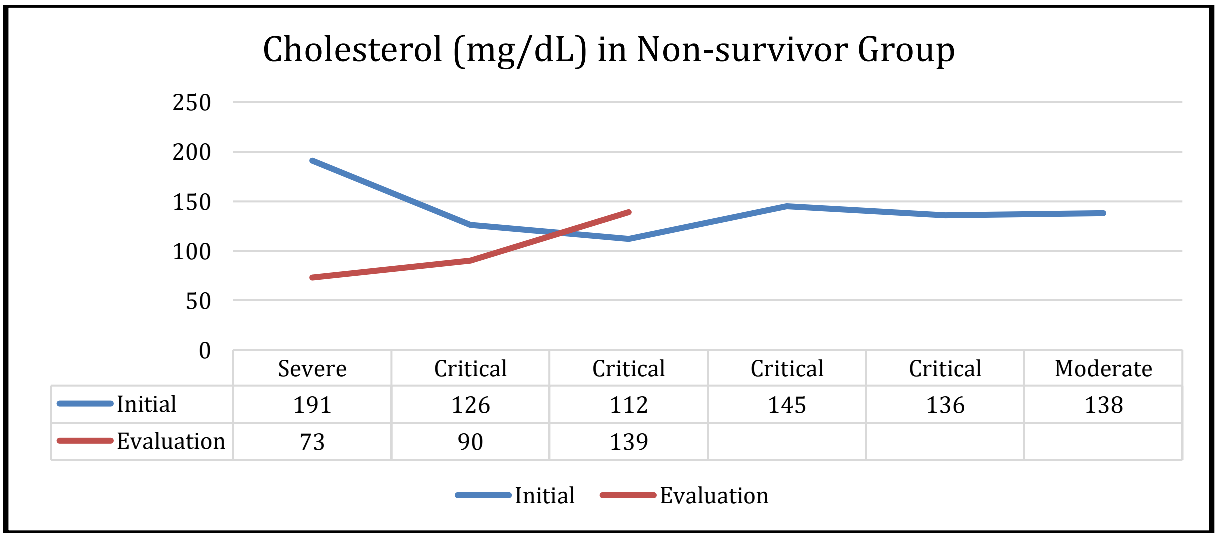
Graphic 1. Cholesterol level according to the severity of COVID-19 patients



Graphic 2. Cholesterol level in survivor and non-survivor of COVID-19 patients



Graphic 3. Cholesterol level in COVID-19 survivors (initial and reevaluation)



Graphic 4. Cholesterol level in the non-survivor group of COVID-19 patients (initial and reevaluation)

DISCUSSION

Recently, dyslipidemia cases were reported in COVID-19 patients, and it shows that cholesterol level decrease is associated with severity level and mortality.[4,5] In a cohort study of 21 patients, lipid profile was examined before the virus infection and during the disease. The patient's cholesterol level, LDL, and HDL decreased when treated in the hospital, and those levels remain low during the hospitalization. Cholesterol and LDL levels return to the baseline of the outpatients. However, a continuous decrease of those levels occurs in non-survivors.[5]

In another cohort study with more samples (n=597), lipid profile data is classified as mild, moderate, severe, or critical.The level of cholesterol and LDL decreased in COVID-19 patients compared to healthy subjects, and the decreased level correlates with the progress of the symptoms.[4]

The possibility of dyslipidemia occurrence in COVID-19 patients because of the side effects of the intervention is very slight as the patient's cholesterol level decreases before the intervention. The patients receive various kinds of medicine during the treatment, and their cholesterol levels improve along with their symptoms.[5] A study of proteomic and metabolism of COVID-19 patients showed massive suppression of metabolism. It included dysregulation of some apolipoproteins (Apo), for example, Apo A1, Apo A2, Apo H, Apo L1, Apo D, and Apo M.[12]

Hypolipidemia is a rare illness caused by multifactorial inheritance, including genetic alterations and other secondary factors. Hypolipidemia is frequently asymptomatic and is discovered during a lipid profile screening test. In COVID-19, it was stated that the decrease in lipid levels was most likely the result of SARS-CoV-2 infection with a complex pathological process. Because there is no consented limit for cholesterol levels, it is referred to as hypolipidemia.[9]

The cholesterol level that is mainly used for hypolipidemia is 120-150 mg/dL. Several other studies used the median or cut-off obtained in their research.[9,13] There are three causes of primary hypolipidemia that rarely occur abetalipoproteinemia, hypobetalipoproteinemia, and chylomicron retention disease. Secondary hypolipidemia occurs more often and may be caused by acute or chronic infection, malabsorption, malnutrition, anemia, critical illness, chronic inflammation, malignancy, hyperthyroidism, chronic liver disease, and the effect of therapy with statin.[13,14]

In acute or chronic bacterial infection, viral infection and parasite infection may cause hypolipidemia/ hypocholesterolemia because of the pro-inflammatory cytokine effect on lipoprotein metabolism.[15] In 2012, Metwally et al. reported a preliminary report about hypocholesterolemia at the patient with TB.[16] Since then, hypercholesterolemia is often found during the acute phase of bacterial infection.[15]

These changes are mediated by various pro-inflammatory cytokines such as Interleukin (IL)-1, IL-6, and Tumour Necrosis Factor (TNF) alpha involved during the acute phase in sepsis.[17]

For critically ill patients, the decreased cholesterol level marks the presence of infection. A recent cross-sectional study demonstrated the importance of lipid changes in sepsis and found low plasma lipid levels but could not determine whether these were pathogenic findings, reflecting more severe severity or higher microbial burden and lipopolysaccharides (LPS) levels. Cholesterol may play a role in host defense in sepsis, as suggested by the observation that circulating lipids and lipoproteins bind to and neutralize endotoxins.[18]

Some researchers believe that hypocholesterolemia is a more sensitive marker of infection presence than leukocytosis.[15,19] Besides that, hypocholesterolemia is significantly correlated to the acute phase in sepsis in line with CRP level.[17]

Other studies about cholesterol and viral infection also reported, such as hepatitis and dengue infection. Lipid levels are altered in HCV patients, regardless of day infection. In studies in acute HCV patients, LDL and total cholesterol levels were linked to early infection.[19,20] In Hepatitis B, chronic infection with cirrhosis, LDL, and HDL level decrease seems to happen.[21] Lima et al. found a decrease in total serum level of cholesterol and LDL in patients with dengue infection.[22]

Several cases above described Pregnant women who were going on cesarean sections with asymptomatic and mild-moderate COVID-19. Laboratory test results show a high level of the lipid profile of the patients. Dyslipidemia is predicted to correlate with the severity level of COVID-19 but is a dyslipidemia condition in pregnant women related to the severity of COVID-19. Pregnancy in healthy women occurs when a normal change of fat metabolism benefits fetus growth and development, thus increasing lipid levels. Deposition and maternal adipose hypertrophy occur during the first trimester of pregnancy due to an increase in insulin receptor expression.[23]

The increased maternal insulin, besides progesterone production, causes lipogenesis with reduced lipolysis, lipid production increases which then being transported to the fetus through placenta for fetus growth. This change is generally non-atherogenic, and lipid profile level will decrease to pre-pregnancy level after birth.[23] Dyslipidemia in pregnancy may risk premature birth, hypertension in pregnancy, preeclampsia, and gestational diabetes. These risks increase in high triglyceride, low HDL, and small dense-high LDL atherogenic fraction. As a result, the risk of cardiovascular disease will increase.[24,25]

Pregnant females with asymptomatic and mild-moderate COVID-19 in this case series were allowed to be discharged, no complications associated with dyslipidemia such as premature birth, hypertension, preeclampsia, and gestational diabetes were noted.There is a study about characteristics of the pregnant females with COVID-19 in Wuhan, from 118 pregnant females, 109 of them were mild-moderate (92%), and nine were severe to critical (8%).[26]

No data supports the severity level increase of COVID-19 in pregnant females.[3] Another study by Zhu et al. reported that clinical manifestations of the pregnant females with confirmed COVID-19 were similar with the non-pregnant females with COVID-19 infection and had relatively good clinical outcomes.[27,28] Our case series showed no clear relationship between dyslipidemia in pregnant women with the severity of COVID-19.

From the non-survivor group, two patients had a significant decrease in cholesterol level compared to the initial examination. The other five patients had low cholesterol levels (<150 mg/dL) from the beginning.

In four mild-moderate survivors, initial cholesterol levels were>150 mg/dl, and there was no decrease until <150 mg/dl. Meanwhile, one moderate COVID-19 patient with initial cholesterol <150 mg/dl increased to >150 mg/dl. In two survivors with severe/critical infection who had initial cholesterol <150 mg/dL and increased during evaluation, while three other patients from the beginning had initial cholesterol above >150 mg/dL.

Based on this data, cholesterol levels tend to be low in patients with poor prognoses. Non-survivor who already had high levels of cholesterol also experience progressive declines. Meanwhile, mild-moderate patients showed high initial cholesterol level and did not decrease during observation. Those with low cholesterol levels showed elevation during observation.

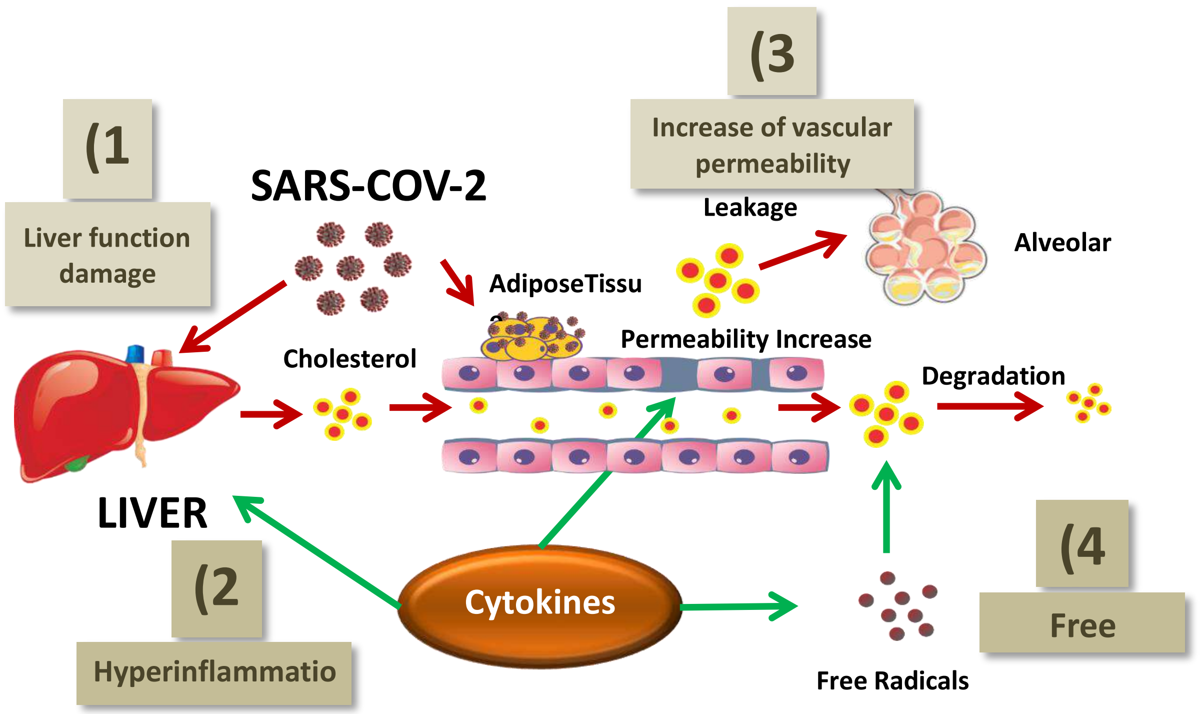


Figure 1. Mechanism of dyslipidemia in COVID-19[29]

The dyslipidemia condition in COVID-19 is interesting; some mechanisms assumed to play roles in the occurrence of dyslipidemia in COVID-19 showed in Figure 1.[29] Damage to liver function occurs as a result of SARS-COV-2 infection, which can interfere with LDL uptake and reduce cholesterol biosynthesis. However, AST and ALT only show a slight increase in less than 50% of the patients.[4,5,30]

This minimal increase of AST and ALT does not accurately describe the liver's LDL uptake and cholesterol biosynthesis ability. As shown in some cases explained previously, the increase of AST and ALT does not always occur in patients with dyslipidemia. Sterol regulatory-element binding protein (SREBPs) is the main transcription factor that manages the expression of various enzymes needed for lipid synthesis. Intracellular lipid homeostasis is regulated by the endoplasm reticulum, where on its membrane there is SREBP cleavage-activating protein (SCAP), squalene monooxygenase (SM), and nuclear factor erythroid two related factor-1 (Nrf1).[31]

When the body needs cholesterol, SCAP will bind SREBPs in the endoplasm reticulum, deliver it to Golgi, and facilitate SREBPs proteolysis to produce the factor domain release of SREBP transcription the entry of the nucleus to increase cholesterol synthesis and uptake. It is very reasonable to speculate that cholesterol synthesis and uptake path has changed in COVID-19 patients because recently, there is evidence that SARS-CoV-2 can suppress the amount of protein associated with the cholesterol mechanism.[12,30]

The hyper-inflammatory response generated by SARS-CoV-2 infection alters lipid metabolism. Inflammatory cytokines such as TNF alpha, IL-6, and IL-1 beta have been proven to change lipid composition, function, and transportation in HIV patients.[32] Cytokines storm in COVID-19 is considered mortality-causing factor in COVID-19 patients. Interleukin-6 increases to 96% of patients in the research of Fan et al.[11] It shows that cytokines may contribute to LDL abnormalities in COVID-19 patients.[5] In some cases that have been described above, cholesterol level decrease is correlated with the inflammatory level that occurs, which is marked by the increase of NLR, CRP, LDH, and Ferritin.[3]

The increase of vascular permeability in SARS-CoV-2 infection causes cholesterol leakage to the alveolar and forms exudate that contains proteins and cholesterol.[29] Exudate has been found in the pulmonary autopsy of SARS patients, such as in pulmonary pathology of COVID-19 patients.[33]

Free radicals are commonly increased in viral infection.[5] It fastens lipid degradation in COVID-19. Oxidized LDL examination is needed to confirm this possibility. Besides that, cholesterol facilitates SARS protein S bonded with Angiotensin Converting Enzyme (ACE) 2 for entering into the target cells. Adipose tissues may function as a reservoir for SARS-CoV-2.[29,34]

There were some limitations in this case series. First, this case report only explains some cases that cannot describe the complete profiles of COVID-19 patients in Ulin Regional Hospital Banjarmasin yet. It needs further research of a bigger scale to prove the correlation between cholesterol level with severity level and mortality of COVID-19 patients and find the roles of cholesterol in SARS-CoV-2 infection. Second, equal treatment among groups should also be noticed regarding the disease onset with the time of cholesterol examination, cholesterol evaluation examination schedule, and the time of cholesterol sample taking. Third, viral load examination may help to determine the virulence level of SARS-CoV-2 and whether it is related to the patients' cholesterol level.

CONCLUSION

This study showed several cases of a higher cholesterol level in asymptomatic and mild-moderate COVID-19 survivors compared to severe-critical and non-survivors. Cholesterol is thought to play an important role in the pathological development of COVID-19 and was thought to be associated with severity and mortality, which requires further studies.

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Endobronchial Tuberculosis: Diagnosis and Treatment Approach

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Abstract

Endobronchial tuberculosis (EBTB) is defined as tuberculosis (TB)infection of the tracheobronchial tract. Tracheal and bronchial involvement from TB infection was first reported by Morten in 1698. Endobronchial tuberculosis is a form of TB that is difficult to diagnose because the lesions are frequently undetectable by sputum examination and chest X-ray alone. Endobronchial tuberculosis is present in 10-40% of active TB patients and more than 90% of cases are accompanied by bronchial stenosis of various degrees. The main goal of therapy in active EBTB is to eradicate *Mycobacterium tuberculosis* in the tracheobronchial tract and further prevent stenosis. Complications of EBTB apart from airway stenosis are atelectasis, haemoptysis and shortness of breath accompanied by wheezing even after administration of anti-tuberculosis drugs (ATD).

Keywords: atelectasis, EBTB, TB

INTRODUCTION

Tuberculosis (TB) is still a global health issue, as well as the leading cause of death from infectious diseases. In 2019, there were 10 million new TB cases reported, with roughly 1.5 million fatalities from the disease.[1]

Endobronchial tuberculosis (EBTB) is defined as TB infection of the tracheobronchial tract. Tracheal and bronchial involvement from TB infection was first reported by Morten in 1698. Endobronchial tuberculosis is a form of TB that is difficult to diagnose because the lesions are frequently undetectable by sputum examination and chest X-ray alone. Even after the development of efficient TB therapy, EBTB remains a major health issue due to the frequently delayed diagnosis. Complications of EBTB are airway stenosis, atelectasis, haemoptysis and shortness of breath accompanied by wheezing even after administration of anti-tuberculosis (ATD) drugs.[2,3]

Endobronchial tuberculosis is present in 10-40% of active TB patients and more than 90% of cases are accompanied by bronchial stenosis of various degrees. The main goal of therapy in active EBTB is to eradicate *Mycobacterium tuberculosis* in the tracheobronchial tract and to further prevent stenosis. To prevent complications that can increase morbidity and mortality, prompt diagnosis and therapy are needed. This literature review discusses the signs and symptoms, pathogenesis, diagnosis and therapy of EBTB [4,5]

EPIDEMIOLOGY

The incidence of EBTB cannot be determined with certainty, especially since bronchoscopy is no longer a routine examination in pulmonary TB cases. In a 1943 investigation, it was discovered that the proportion of EBTB was 15% in pulmonary TB cases using rigid bronchoscopy and 40% in autopsy results.[4]

According to numerous research, the incidence of EBTB after the introduction of anti-tuberculosis therapy ranged from 6 to 40%. Su et al reported an incidence of EBTB, which was 23.9% of 1,442 pulmonary TB patients, with a higher proportion of females aged <50 years than males. EBTB cases are reported to occur more frequently in females, for reasons that are unknown with certainty, but it is possible that this is due to females tend to cough up less from preconceptions for socio-cultural and aesthetic reasons, allowing them to be exposed to tubercles containing mycobacteria for longer because the anatomical structure of the bronchial anatomy of females are narrower than that of males, allowing them to be exposed to tubercles containing mycobacteria for longer.[5–7]

EBTB is most common among people in their twenties. Aniwidyaningsih et al discovered that 86.7% of the 30 EBTB patients studied were females, with a mean age of 28 years.

PATHOGENESIS

Although the exact pathogenesis of EBTB is unknown, five mechanisms are thought to play a role in its occurrence: (1) direct spread of the focus of infection in the lung parenchyma; (2) direct attachment of mycobacteria from infected sputum; (3) hematogenous spread; (4) erosion of lymph nodes into the bronchi; and (5) lymph flow from the parenchyma to the peribronchial region.[3,4,7,8]

Endobronchial tuberculosis can affect all bronchial branches, but the main location is the main bronchi, bilateral superior lobe and middle lobe. Since the left main bronchus is structurally more constricted by the aortic arch and mediastinal lymph nodes, infection in the lymph nodes spreads more rapidly to the left bronchus than to the right bronchus.[9] Endobronchial tuberculosis (EBTB) is classified as single if it is detected only in one location in the trachea, main bronchus, or lobar bronchus, multiple if it is found in two or more bronchial branches, and central if it affects the proximal part of the bronchus. This location is susceptible to stenosis.[7,8]

Pathologically, EBTB can affect the entire tracheobronchus layer, including the muscularis laminae and cartilage. Pathological alterations that develop include mucosal and submucosal TB infections, ulcers, granulomas, fibroplasia, and tracheobronchial stenosis. Pathological changes begin with the occurrence of hyperemia in the mucosa and submucosa due to infiltration of inflammatory cells, especially lymphocytes, then followed by the formation of tubercles accompanied by caseous necrosis which in turn will cause ulcers in the mucosal lining of the bronchi. The ulcer develops on the lining of the tracheobronchus wall and the ulcer becomes deeper, resulting in the formation of polyps towards the bronchial lumen. At an advanced stage, hyperplasia, fibrosis, and contractures develop, eventually leading to tracheobronchial stenosis.[2,5,10]

CLINICAL

Clinical signs and symptoms are typically nonspecific, such as a dry or productive cough, haemoptysis (rarely massive), sternal or parasternal chest discomfort, and shortness of breath due to pulmonary atelectasis. Persistent cough is one of the most common respiratory symptoms in 70-80% of EBTB patients.[11]

Systemic TB symptoms such as decreased appetite, weakness, and fever are not prominent in EBTB. Sud et al found that a persistent cough lasting 4 weeks in young females is a predictor of EBTB and tracheobronchial stenosis, hence a bronchoscopy should be performed right away.[6] Lung examination can reveal diminished breath sounds, isolated wheezing, and crackles.[5,6,12] Liu et al reported late EBTB cases with pleural effusion as a clinical symptom.[13]

DIAGNOSIS

Because of its atypical signs and symptoms, EBTB is more difficult to diagnose than pulmonary TB. The clinical outcomes of EBTB will benefit substantially from early identification and adequate care. A sputum examination was performed first, followed by bronchoscopy and radiographic evaluation.

Sputum Examination

Sputum examination is an important initial examination for the diagnosis of EBTB. Examination of Acid fast bacilli (AFB) sputum gives varying results ranging from 16-53%, but a negative result does not exclude the presence of EBTB. Sputum examination by molecular rapid test (is said to give better results than AFB sputum. Zhang et al[14] found that in 61 EBTB patients, the specificity of genXpert was 100% as compared to microscopic sputum, bronchial swab swabs, sputum, and tissue culture, which were 13.1%, 32.8%, and 68.9%, respectively.

Bronchoscopy

A 22-year-old female with full-term pregnancy and asymptomatic COVID-19 was referred to Ulin Regional Hospital Banjarmasin for cesarean section surgery. BMI was 21 kg/m^2, and blood pressure was 110/70 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Laboratory test result was RBS 116 mg/dl, NLR 3.16%, ALC 1657/ul, CRP 4.2 mg/L, LDH 181 U/L, Ferritin 22.20 ng/mL, D-dimer 6.63 mg/L, AST 25 U/L, ALT 11 U/L, Cholesterol 263 mg/dL, Triglyceride 114 mg/dL, LDL 244 mg/dL, and HDL 38 mg/dL. The patient was declared cured after 27 days of treatment.

Bronchoscopy is a critical tool for detecting EBTB as early as possible. Procedures in bronchoscopy such as biopsy, brushing, rinse, needle biopsy and endobronchial ultrasound (EBUS) can be used to make the diagnosis.[15] A biopsy can yield a positive result in the range of 30.35%-84%.[1,2,5,8] According to a Chinese study, bronchial brushing provided favorable effects up to 84.88%, while bronchial rinses had positive results ranging from 10 to 37.5%.[3] Bronchoscopy is also important to rule out several other disorders such as malignancy and diseases that show other granulomatosis features such as pulmonary mycosis and sarcoidosis.[16]

(A) Caseosaactive, looks hyperemic and the tracheobronchial walls covered with a yellowish-white cheese-like material, seen in 43% EBTB;
(B) Hyperemia-edema shows tracheobronchial mucosal features that are heavily edematous and hyperemic, occurring in 14% of EBTB;
(C) Fibrostenotic shows a narrow tracheobronchial lumen due to fibrosis hyperplasia and contracture, occurring in 10.5% EBTB;
(D) Tumorous showing an intraluminal mass image occurred in 10.5% EBTB;
(E) Granular shows a hyperemic tracheobronchial mucosal appearance and there are nodules that look like grains of rice (11%);
(F) Ulcerative shows an ulcerated tracheobronchial mucosa (3%);
(G) Nonspecific bronchitis in the form of tracheobronchial mucosal features with mild to moderate edema and/or accompanied by hyperemia (8%).

This picture is shown in Figure 1.

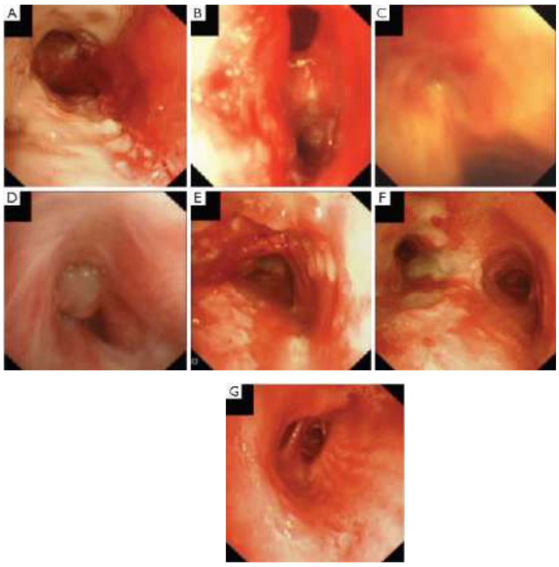

Figure 1. Bronchial mucosa EBTB on bronchoscopy A. caseosaactive; B. hyperemisedema; C. fibrostenotic; D. tumorous; E. Granular; F.ulserative; G. non-specific bronchitis[6]

The mucosal appearance on bronchoscopy can be used to determine the likelihood of stenosis. Despite 3 months of anti-tuberculosis therapy, edematous, hyperemic, fibrostenotic and tumorous mucosal features are more likely to develop bronchial stenosis or blockage. The granular subtype had the highest level of positivity for microscopic examination and M. tuberculosis culture based on the results of the bronchoalveolar lavage (BAL) examination, while the fibrostenotic and nonspecific types had more frequently negative results.[5,9,17,18]

Lymph nodes enlargement is often seen on bronchoscopic examination, appears in the form of a grayish yellow mass on the bronchial mucosa, Lymph nodes often appear to be ulcerated, bleeding and forming granulation fistulas.[4,10]

Radiology

Approximately 10-20% of EBTB patients may show normal images on chest radiograph. Infiltrates in the lung parenchyma of the afflicted lobe are the most prevalent chest X-ray image in EBTB. Features of segmental or lobar collapse, as well as lobar hyperinflation, may also be present. Fibrotic, calcification, bronchiectasis, hillar lymphadenopathy, and pleural effusion are abnormalities that can be found.[2,8,13]

Chest Computed Tomography (CT) examination provides more detailed information than chest X-ray such as stenosis, nodules, cavities, pleural effusions and mediastinal lymphadenopathy. Ho et al[11] in their case report reported asymmetric hilar features that should be suspected as a sign of EBTB. Several studies have shown that 95-97% of EBTB can be seen on chest CT. Chest CT examination reveals a centrilobular asymmetric spot or nodule and tree in buds appearance. This features were distributed unilaterally as well as bilaterally. Bronchoscopy or microbiological testing must be performed on patients whose CT examination results indicate EBTB.[3,6,9,19]

COMPLICATIONS

Bronchial stenosis and stricture are the most common complications of EBTB. This complication is irreversible despite adequate ATD administration. Bronchosthenosis occurs in about 60% of cases and affects the main bronchi. A poor clinical outcome may arise due to airway obstruction, which may also affect the trachea.[18,19]

Brochiectasis is also a frequent complication of EBTB, usually as a result of paracicatrial processes, destruction and pulmonary fibrosis. Bronchiectasis that occurs is often asymptomatic and usually found in the upper lobe of the lung and if there are complaints, haemoptysis is the most common complaint experienced by patients.[2,5]

DIFFERENTIAL DIAGNOSIS

Lung cancer is the most important differential diagnosis that must be considered. Some of the other differential diagnoses are inflammation, sarcoidosis, asthma, atelectasis, foreign body aspiration, recurrent pneumonia and actinomycosis.[3,6,12,13]

Sarcoidosis is also a disorder that can affect endobronchial and has a clinical appearance very similar to EBTB. Bronchostenosis due to sarcoidosis is in some cases are very similar to EBTB and should be distinguished carefully. Patients with HIV AIDS should consider Kaposi's endobronchial sarcoma as the cause.[3,4]

THERAPY

The stage of the disease must be considered in EBTB management. First, it must be determined whether the disease is active or in a fibrotic condition, which is quiescent but might develop bronchial stenosis. The goal of treatment during the active period is to eradicate *M. tuberculosis* and to prevent tracheobronchial stenosis. Tracheboronchial strictures can occur despite administration of ATD and intralesional silver nitrate administration. EBTB is treated in the same way as pulmonary TB, with first-line ATD (rifampin, isoniazid, ethambutol, pyrazinamide, and streptomycin) for 6 to 9 months.[4,5,20]

Another therapeutic modality used are corticosteroids. Corticosteroids have long been used as an adjuvant to EBTB treatment, but their use is debatable. Corticosteroids may be beneficial in the early stages of EBTB because hypersensitivity was the predominant at the time, but they have minimal effect in the advanced stages.[18]

Corticosteroids have also been tested intralesionally. Rikimaru[20] demonstrated that combining streptomycin 100 mg, dexamethasone 0.5 mg, and naphazoline 0.1 mg twice day with regular ATD resulted in faster healing of lesions and less bronchial stenosis. In another study, submucosal injection of methylprednisolone also showed resolution of EBTB. To date there has been no comprehensive and systematic evaluation of the use of cortiosteroids as adjunctive therapy in EBTB. Um et al[19] showed that age> 45 years, fibrostenotic subtype EBTB and duration of symptom with ATD administration of> 90 days were predictors of persistent tracheobronchial stenosis.

The complication of EBTB is bronchial stenosis which can lead to atelectasis and obstructive pneumonia. Usually, there are complaints of shortness of breath and wheezing. Because steroids cannot reverse bronchial stenosis, airway patency must be re-established through bronchoscopy or surgery. Bronchoscopy techniques include laser, argon coagulation, cryotherapy, and balloon bronchodilation.[1,8,9]

These strategies can be used separately or in tandem. The main indication for laser bronchoscopy is the presence of tracheal, main bronchial, and lobe obstruction, which results in decreased ventilation and severe symptoms such as shortness of breath, stridor, and haemoptysis. Bronchoscopy with balloon dilation is a minimally invasive and relatively safe procedure using flexible bronchoscopy. This is accomplished by inflating a balloon inside a bronchus with a stricture. This approach is better suited for circular cyclic stenosis and chronic stenosis than stenosis with active inflammation, calcification, and damaged cartilage (malacia).[21] The success rate of this procedure has been found to range between 6.3%-73%. If balloon dilation fails to resolve the stenosis, a stent should be inserted as soon as possible.

The stent used is usually made of silicon (Dumon stent). Metal stents (Ultraflex and Gianturco stents) should be avoided because it is difficult to remove it again.[3]

Iwamoto et al[21] report the success of maintaining long-term airway patency with the use of Dumont stents. tubular and Y) in 6 EBTB patients. Iwamoto reported that the use of Ultraflex stents caused more granulation tissue than the use of click stents. The complications of bronchial stent placement are airway perforation, stent changing position and location, granuloma obstruction due to stents which can result in emphysema, pneumothorax, pneumomediastinum, mediastinitis, shortness of breath and haemoptysis.

Low et al[21] described immediate and long-term clinical recovery in 7/11 (63.6%) patients treated with Dumon stents. Similar successful findings were observed by Ryu et al[21] to 75 patients with tracheobronchial tuberculous stenosis. Independent factors such as granulation tissue expansion and tracheobronchial malacia indicate a bad prognosis in stent insertion.

A new technique has been described recently to prevent stenosis from recurring after dilation. Mitomycin-C, which is an antineoplastic agent that inhibits fibroblast proliferation and modulates wound healing and scar tissue, is administered topically with saturated serum applied by forceps biopsy (0.4-0.5 mg/ml) in some cases, as an adjunct therapy for bronchoscopy procedures. [21]

Other brnchoscopy interventions are ablative techniques including heat therapy (laser therapy, electrocautery, and argon plasma coagulation (APC)) and cyrotherapy. Laser resection is based on laser energy sent through a rigid and/or flexible bronchoscope. Direct laser therapy recommended for endobronchial malignant lesions but also for EBTB-related stenosis. Cavaliere et al[21] treating six patients with tracheobronchial stenosis TB: Normal bronchial patency was not fully achieved, but ventilation was significantly increased. The successful administration of Nd-YAG laser therapy was also described by Low et al[21] and Ryu et al[21] who cutting the fibrous band in 21 and 13 patients with TB stenosis, and by Lim et al[21] who treated 14 web-like stenosis before stent placement.

Bronchial stenting can serve as a temporary therapeutic intervention. This is followed by successful stent removal without the need for reintervention.[9] Bro Argon Plasma Coagulation is a safe method to be done in cases of tumorous EBTB to prevent luminal stenosis. Jin et al[21] describing the long-term outcomes of 41 patients with EBTB exposed to APC and TB drugs compared to a control group receiving antibiotics only. Cryotherapy, which results in cyclical and repeated cold-induced cell death is a safe approach to treating TB stenosis without the risk of airway fire or bronchial wall perforation. stenosis in 12 patients with post-TB stenosis.

Recently, Mu et al[21] found that bronchoscopic cryotherapy could increase granular EBTB and prevent progressive stenosis. They evaluated 38 patients treated with flexible instrument cryotherapy and anti-TB drugs compared with 38 patients who received only anti-TB drugs. Treatment success rate is 100% in cryotherapy arm affected by a mean of 4 applications per patient vs. 78.9% in those treated only with anti-TB drugs. Recovery time was faster in the cryotherapy-treated sections and there were no reports of severe side effects. Cryosurgery is another safer option than balloon and laser dilatation. The risk of bronchial perforation in cryosurgery is smaller than other procedures but this procedure requires repeated procedures so it can take longer. Li et al[14] reported successful bronchoplasty in 8 EBTB patients who experienced pulmonary atelectasis due to EBTB even though they had been given OAT for a long time. The success of the bronchoplasty performed by Li et al shown in Figure 2.

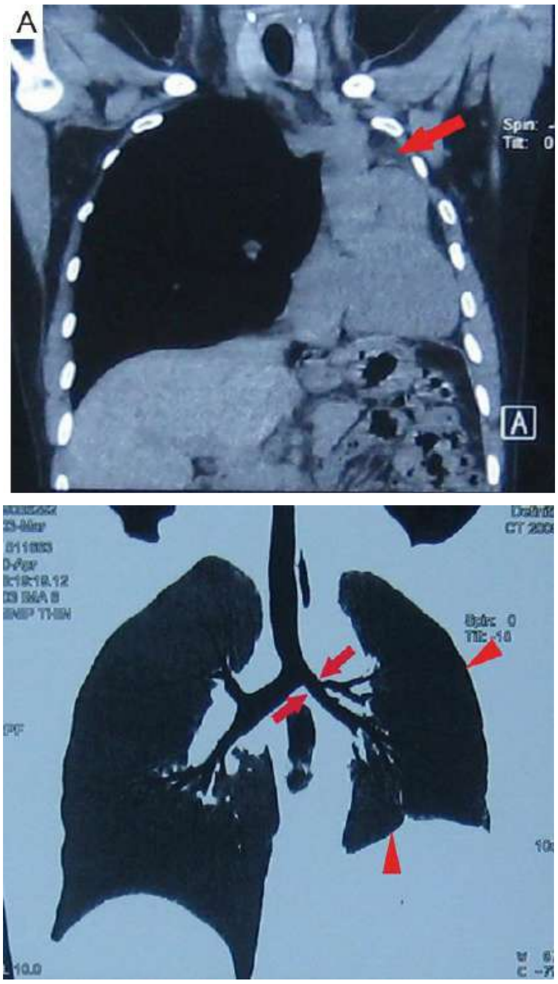

Figure 2. Pre and Post bronkoplasti[14]

Severe tracheobronchial stenosis that causes lung collapse, pulmonary infection and recurrent haemoptysis requires surgery such as pneumonectomy or lobectomy.[22] A study conducted by Lei et al[22] showed that of 25 EBTB patients who underwent surgery, almost all were females, young with the fibrostentotic type. Cough was the most common complaint. Surgery is an option for EBTB patients with severe bronchostenosis. The most common surgical methods are lobectomy or multilobectomy followed by pneumonectomy and bronchial sleeve resection.[2,5,7]

The final method was performed on strictures in the main bronchus near the upper lobe. There was no postoperative death, but found atelectasis, atrial fibrillation, empyema as postoperative complications. Several different studies conducted showed that post-lobectomy and pneumonectomy complications ranged from 15.3-23.8%. A dangerous post-resection complication is bronchopleural fistula with a mortality rate of up to 40% and the main causative factor is active local infection, therfore one way to prevent complications of bronchopleural fistula is to delay surgery as long as there are signs of acute infection in the bronchi.

CONCLUSION

Endobronchial tuberculosis is a rare form of TB. It is more common among young females, and the cause is unknown. Because of the atypical clinical symptoms of TB, the diagnosis of EBTB is sometimes delayed until the development of complications from severe bronchial stenosis. Bronchoscopy is the main diagnostic approach combined with radiological, microbiological and histopathological examinations. ATD is administered along with single or recurrent bronchial dilatation, and is frequently combined with laser, argon plasma coagulation, cryotherapy, and balloon bronchoplasty performed by bronchoscopy. If the stenosis is severe, surgical procedures such as lobectomy or pneumonectomy are undertaken.

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Chest Wall Syndrome

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Abstract

Chest wall syndrome is the most frequent cause of chest pain complained by patients admitted to the physician's office, in outward as well as in emergency department. It may affect all ages with sex ratio of 1:1 between man and woman. History of illness and sensibility to palpation or tenderness were the keys to the diagnostic approach. Pain was generally moderate, well localized, continuous or intermittent over a number of hours to days or weeks and was amplified by position or movement that was commonly located on the left side of the chest. Chest wall syndrome is usually a common and benign condition, but it leads to anxiety and frequent recurrence. Definitive treatment is not yet confirmed and treatment for the different condition causing isolated musculoskeletal chest pain is poor. Therefore, some options to avoid aggravating physical activities, stretching, and simple analgesics as needed are the best choices of current management.
Keywords: aggravating activities, chest wall syndrome, tenderness

INTRODUCTION

Chest wall syndrome is the most frequent cause of chest pain admitted in the physician's office in outward as well as in emergency department. However, the situation remains poorly recognized, particularly in the outward department. The chest wall contains a range of bony and soft tissue structures, including the spine therefore it may be difficult to pinpoint the exact source of pain in an individual patient. Costochondritis, anterior chest wall syndrome, atypical chest pain or musculoskeletal pain syndrome are some of the terminologies described for the condition above. The etiology of chest wall syndrome are varies, from light to life-threatening conditions accompanied by anxiety that may beyond the heart attack sensation as the patient thought to have a cardiovascular disease and daily activity impairment.[1–3]

Chest wall syndrome prevalence are 20% to 46.6% cases in outward department and only 6.2% cases were admitted to the emergency department. A systematic review result that most chest pain (56%) was acute coronary syndrome, and the rest (44%) was non-specific chest pain in origin. In most patients, pain was localized in the retrosternal area, and/or on the left side without temporal association. Complaints of pain is continued after 6 months. Localized muscle tension, stinging pain, palpable pain, and the absence of cough all contribute equally to a simple four-point score that can be used to include or exclude the diagnosis. However, the high prevalence is not yet compared with comprehensive definitive therapy. Indonesia's data specific to chest pain shows that it mostly caused by malignancy.[1–3]

CHEST WALL

The thoracic wall consists of a bony framework held together by twelve thoracic vertebrae posteriorly that give rise to ribs that encircle the lateral and anterior thoracic cavity. The first nine ribs curve around the lateral thoracic wall and connect to the manubrium and sternum. Ribs 10-12 are relatively short and attach to the costal margins of the ribs just above them and do not reach the sternum.[1–3]

The first seven ribs are true ribs, attach to the manubrium and directly attach to the sternum body. Ribs eight to ten only attach to the inferior part of the sternum via the costal cartilages. Ribs 11-12 are termed floating ribs because they do not attach directly to the sternum. Ribs eight to ten are the false ribs due to a lack of direct attachment to the sternum. At the level of the spine, the ribs articulate with the costal facet of two opposing vertebrae. An articular capsule surrounds the head of each rib and the attachment to the transverse process is made with the help of the radiate ligament. As the ribs leave the vertebrae, they curve around the lateral thoracic wall and approach the anterior wall of the thoracic cavity.[1–3]

The vertical bone of the chest, the sternum, defines the anterior chest wall. The three separate bone segments of the sternum with different sizes and shapes include 1) the thick manubrium, 2) the long body of the sternum, and 3) the xiphoid process. It develops independently of the ribs. In sporadic cases, the sternum may not fully form, and the underlying heart may be exposed. The most superior portion of the sternum is the manubrium, and it is also the first to form during embryogenesis. The sternal body and xiphoid process soon follow the manubrium in development.[1,2]

Anatomically, the manubrium is located at the level of thoracic vertebral bodies T3 and T4. The manubrium is also the widest and thickest segment of the sternum. During a physical exam of the chest, one noticeable feature of the manubrium is the presence of the suprasternal notch. On either side of this notch, one will feel the thick attachment of the clavicles. For access to the superior mediastinum, suprasternal goiter or thymus, some thoracic surgeons will only make a midline incision in the manubrium.[1,2]

The sternal body is located at the level of vertebral bodies T5-T9. It covers a significant portion of the mid-chest and is very strong. The xiphoid process is a thin and very small bone. Its size may vary from two to five centimeters (cm) with a variable shape. The xiphoid may appear bifid, oval or be curved inwards/outwards. In younger individuals, the xiphoid is mostly cartilaginous but is nearly wholly ossified by age 40. By the age of 60 and over, the xiphoid is almost certainly completely calcified. To perform pericardiocentesis safely, the needle has to be placed directly underneath the xiphoid because the heart is just a few fingerbreadths below.[1,2]

The thoracic cavity subdivides into three compartments; the mediastinum and two pleural cavities, one on each side. The mediastinum is the median compartment containing the heart and great vessels, whereas the pleural cavities contain the lungs. The thoracic cage protects the lungs and the heart as well as provides attachments for the muscles of the thorax, upper extremities, back, and abdomen.[1,2]

It communicates superiorly with the neck via the thoracic outlet and inferiorly separates the abdomen from the respiratory diaphragm. The boundaries of the thoracic wall are important landmarks. The thoracic wall is bounded anteriorly by the sternum and costal cartilages; laterally by the ribs and intercostal spaces; posteriorly by the thoracic vertebrae and intervertebral discs; superiorly by the suprapleural membrane and inferiorly by the respiratory diaphragm.[1,2]

There are three intercostal muscles; the external intercostal, internal intercostal, and innermost intercostal muscles. These muscles are present in the intercostal spaces and the intercostal nerves and blood vessels run between them. The most superficial layer is the external intercostal muscle. The external intercostal muscles extend posteriorly from the rib tubercle to the costochondral junction anteriorly, where the anterior (external) intercostal membrane takes the place of the muscle fibers. The internal intercostal muscle forms the intermediate layer. This muscle extends anteriorly from the sternum to the rib cage posteriorly, where the muscle fibers are replaced by the posterior (internal) intercostal membrane. The innermost intercostal muscle forms the deepest layer and is lined internally by the endothoracic fascia, which in turn is lined internally by the parietal pleura.[2,4,5]

Associated within each rib is the intercostal bundle, consisting of the vein, artery, and nerve that travel along the underside of the inferior aspect of each rib. The nerve is the most inferior structure in the bundle and travels within the layers of intercostal muscles. As the nerves continue travelling from posterior to anterior and the innermost intercostal muscle layer thins, the lower intercostal nerves (7-11) are found between the parietal pleura and the posterior aspect of the intercostal muscle, prior to crossing the posterior surfaces of the costal cartilages and continuing to the abdominal wall.[3]

CHEST WALL SYNDROME

Chest wall syndrome/chest wall pain syndrome is a painful condition that manifests as direct or referred pain to the chest wall as a result of stress or injury to the body. There are numerous pathological processes that may result in self-limiting or chronic conditions. The history and examination target the musculoskeletal as well as other systems that may provide diagnostic information for rheumatic or non-rheumatic systemic causes. The chest pain needs to be fully characterised in terms of onset, site(s), radiation, relieving and exacerbating factors (in particular, any relationship to postures, specific activities or acute trauma). Atypical symptoms, such as night pain or severe pain, alert the General Practitioner (GP) to look for systemic causes such as fractures, infection or neoplasms. The presence of other musculoskeletal or other symptoms assists in diagnosis of other conditions.[6,7]

It has been suggested the cause of chest wall syndrome can be grouped into three categories and individual conditions can be broadly considered as more or less common. These are conditions causing isolated musculoskeletal pain, rheumatic diseases, and systemic non-rheumatological conditions.[7,8]

a. Isolated musculoskeletal pain
   1. More common
      a) Costochondritis
      b) Lower rib pain syndrome
      c) Pain from thoracic spine, costovertebral joints
      d) Sternalis syndrome
   2. Less common
      a) Stress fracture
      b) Tietze's syndrome
      c) Xiphoidalgia
      d) Spontaneous sternoclavicular subluxation
b. Rheumatic diseases
   1. More common
      a) Fibromyalgia
      b) Rheumatoid arthritis
      c) Axial spondyloarthritis (including ankylosing spondylitis)
      d) Psoriatic arthritis
   2. Less common
      a) Sternoclavicular hyperostosis
      b) Systemic lupus erythematosus
      c) Septic arthritis of the chest wall
      d) Relapsing polychondritis
c. Non-rheumatic systemic causes
   1. Osteoporotic fracture
   2. Neoplasms
      a) Pathological fracture
      b) Bone pain
   3. Sickle cell diseases (rare)

PATHOGENESIS AND PATHOPHYSIOLOGY

Pathogenesis of chest wall syndrome is not well understood. The whole process relevant with pain sensation is related to the complexity of chest wall anatomy. Bony framework is vulnerable to fracture as well as joints and articulation are vulnerable to injury. Innervation of the thoracic wall arise from intercostal nerves at anterior rami of spinalis nerves. This system is walking along under every rib. Every disruption to rib, rami or any connected fiber may cause pain.[9]

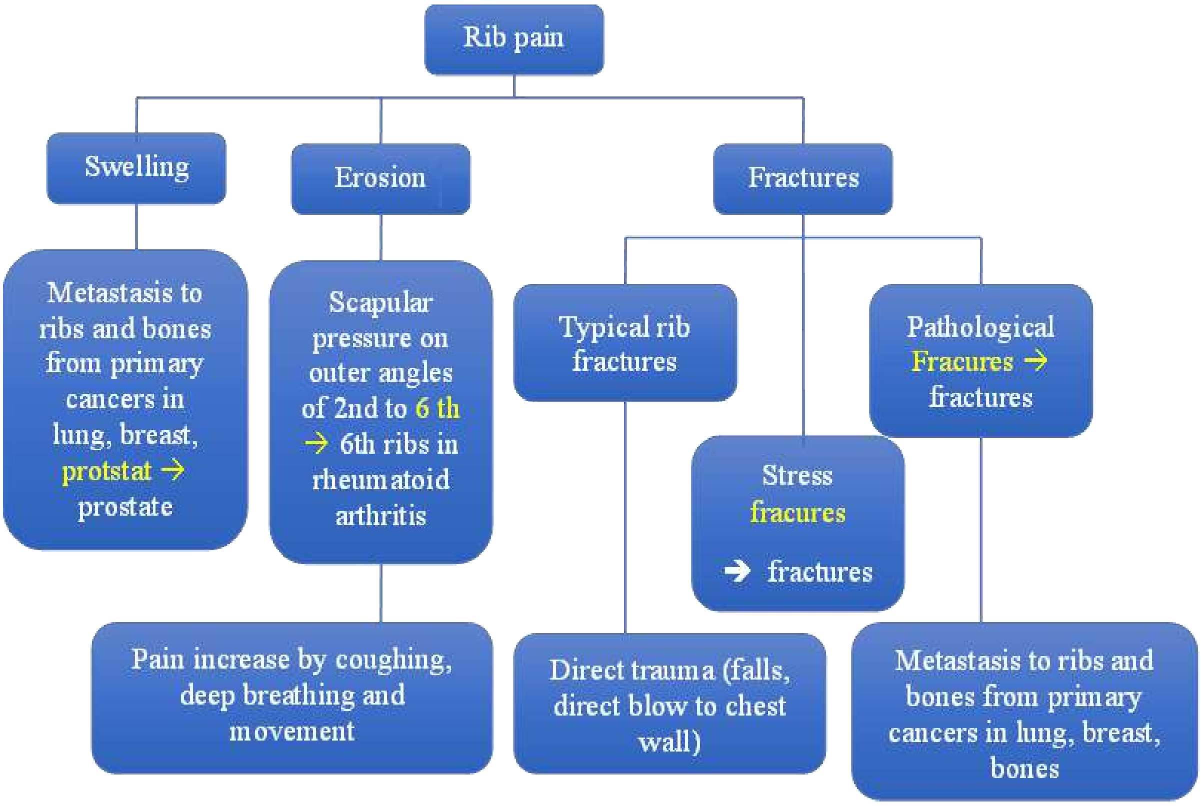

Figure 1. Algorithm causes of rib pain[9]

The visceral pain receptor is found in almost every visceral organs (thorax, pelvis, abdomen) surrounded with connective tissue. Noxious stimuli from this receptor activate the afferent fiber that not protected with myelin and lead to poor local response of pain.[9]

DIAGNOSIS

Musculoskeletal examination includes rib, chest wall, muscles of chest wall, lumbar and vertebrae. The key is to identify location of tenderness by active or passive movements (flexion, extension, lateral flexion and rotation) producing pain. Important areas to palpate are the costochondral joints, sternum, ribs, thoracic vertebrae, intercostal space, paraspinal muscle, trapezius muscle and pectoralis muscle. The palpation is systematically performed to evaluate every structure at each thoracic level such as to palpate centrally over the spinous processes then 2–3 cm laterally on each side (zygapophyseal joints), then transversely on the side of the spinous processes, then 4–5 cm from midline (costotransverse junctions) and, finally, over the posterior ribs.[7]

Ruling out the non-musculoskeletal cause can be accomplished solely by history and physical examination. Common causes and key features of musculoskeletal chest wall syndrome are listed in Table 1. The key features may be required in some instances to complete the diagnostic process. Cough, fever, chest wall swelling, or other respiratory findings on history or examination should have chest radiography.

Table 1. Key feature of common causes of musculoskeletal chest wall pain[7]

Chest Wall Pain	Common Causes
Isolated musculoskeletal chest wall pain	
Costochondritis	Tenderness in multiple areas over the costochondral or costosternal junctions; palpation reproduces the pain, no associated swelling; mostly affects 2nd to 5th ribs.[8]
Lower rib pain syndrome	Pain in the lower chest or upper abdomen with a tender spot on the costal margin; pain reproduced by pressing on the spot.[7,10]
Sternalis syndrome	Localised tenderness over the body of the sternum or sternalis muscle; palpation often causes radiation of pain bilaterally.
Thoracic costovertebral joint dysfunction	Localised pain approximately 3–4 cm from the midline and possibly referred pain ranging from the posterior midline to the lateral chest wall, and anterior chest pain. Movement of the rib provokes pain at the costovertebral joint and reproduces referred pain.[11]
Rheumatic causes	
Fibromyalgia	Widespread musculoskeletal pain and tenderness, poor quality, unrefreshing sleep, fatigue and cognitive disturbances, not accounted for by another condition. Diagnosed by American College of Rheumatology criteria.[12,13]
Rheumatoid arthritis	Swelling and/or tenderness of multiple small and/or large synovial joints, positive for rheumatoid factor and/or anti-citrullinated protein antibody, and abnormal C-reactive protein or erythrocyte sedimentation rate. Diagnosed by American College of Rheumatology criteria.[14]
Axial spondyloarthropathy (including ankylosing spondylitis)	Back pain for 3 months or longer with onset under 45 years of age, together with either: 1) imaging features of sacroiliitis on MRI or X-ray, and one other feature of SpA* 2) HLA-B27 and two other features of SpA*[15]
Psoriatic arthritis	Inflammatory articular disease (joint, spine, or enthesis) with three out of five of the following: 1) evidence of current psoriasis, past history or a family history of psoriasis, 2) current psoriatic nail changes, 3) negative for rheumatoid factor, 4) current or a history of dactylitis, 5) radiographic evidence of juxta-articular new bone formation on plain radiographs of the hand or foot.[16]
Non-rheumatic systemic causes	
Osteoporotic fracture	Acute back pain, loss of height or kyphosis for thoracic spine fractures, acute localised pain for rib fractures corticosteroid uses and other osteoporosis risk factors for both.[17]
Neoplasm with pathological fracture or bone pain	Severe and/or night pain, and associated non-musculoskeletal symptoms.

Note: *SpA, spondyloarthritis: features are inflammatory low back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease, good response to non-steroidal anti-inflammatory drugs, family history of SpA, HLA-B27, elevated C-reactive protein

Imaging of the chest with computed tomography (CT) can delineate pathology in costal cartilages and rule out underlying pathology such as tumors. Routine laboratory testing is not necessary unless the diagnosis is uncertain or if there is a sign of inflammation.[7]

DIFFERENTIAL DIAGNOSIS

It is important to rule out visceral and life-threatening causes of chest pain, such as ischemic heart disease and pulmonary embolism, as well as non-musculoskeletal causes, such as gastro-oesophageal reflux disease, through appropriate clinical assessment and investigations. Current methods for scoring features of musculoskeletal causes of chest pain that differentiate them from cardiovascular causes have had inadequate diagnostic performance. The clinician's thorough assessment, therefore, remains the best approach. In particular, the localisation of pain and presence of chest wall tenderness or reproduction of pain by movements are insufficient to justify ruling out serious non-musculoskeletal causes.[9]

TREATMENT

Specific treatment has not been established. The treatment approach is directed at pain relief with asetaminofen, nonsteroidal anti-inflammatory drugs when safe and appropriate, or other analgesics. Heat compresses or pads may help, especially in the case of muscle overuse. Minimizing activities that provoke the symptoms, like reducing the frequency and intensity of the activities, are also helpful. In some condition, physical therapy has also applied for persistent musculoskeletal chest pain. Stretching, exercise, mobilization and soft tissue therapy as well as fixing the body posture. Severe cases like in persistent pain, particularly at night and early in the morning, may be treated with administration of local injections of idocaine and corticosteroid into areas with severe pain, which is a necessary.[8]

Table 2. Differential Diagnosis and Treatment of Chest Wall Syndrome[8]

Diagnosis	Diagnostic consideration	Treatment
Arthritis or sternoclavicular, sternomanubrial, or shoulder joints	Tenderness to palpation of specific joints of the sternum; evidence of joint sclerosis can be seen on radiography.	Analgesics, intra-articular corticosteroid injections, physiotherapy.
Costochondritis	Tenderness to palpation of costochondral junctions; reproduces patient's pain; usually multiple sites on same side of chest.	Simple analgesics; heat or ice; rarely, local anesthetic injections or steroid injections.
Destruction of costal cartilage by infections or neoplasm	Bacterial or fungal infections or metastatic neoplasms to costal cartilages; infections seen post-surgery or in intravenous drug users; chest computed tomography imaging useful to show alteration or destruction of cartilage and extension of masses to chest wall; gallium scanning may be helpful in patients with infection.	Antibiotics or antifungal drugs; surgical resection of affected costal cartilage; treatment of neoplasm based on tissue type.
Fibromyalgia	Symmetric tender points at second costochondral junctions, along with characteristic tender points in the neck, back hip, and extremities, and widespread pain.	Graded exercise is beneficial; cyclobenzaprine (Flexeril), antidepressants, and pregabalin (Lyrica) may be beneficial.
Herpes zoster of thorax	Clusters of vesicles on red bases that follow one or two dermatomes and do not cross the midline; usually preceded by a prodrome of pain; postherpetic neuralgia is common.	Oral antiviral agents (e.g., acyclovir [Zovirax], famciclovir [Famvir], valacyclovir [Valtrex]); analgesics as needed for pain; may require narcotics or topical lidocaine patches (Lidoderm) to control pain.

Diagnosis	Diagnostic consideration	Treatment
Painful xiphoid syndrome	Tenderness at sternoxiphoid joint or over xiphoid process with palpation	Usually self-limited unless associated with congenital deformity of xiphoid; analgesics; rarely, corticosteroid injection.
Slipping rib syndrome	Tenderness and hypermobility of anterior ends of lower costal cartilages causing pain at lower anterior chest wall or upper abdomen; diagnosis by "hooking maneuver": curving fingers under costal margin and gently pulling anteriorly - a "click" and movement is felt that reproduces patient's pain.	Rest, physiotherapy, intercostal nerve blocks; or, if chronic and severe: surgical removal of hypermobile cartilage segment.
Tietze syndrome	A single tender and swollen, but non-supportive costochondral junction; usually in costochondral junction of ribs two or three.	Simple analgesics; usually self-limiting; rarely, corticosteroid injections.
Traumatic muscle pain and overuse myalgia	History of trauma to chest or recent new onset overuse myalgia of strenuous exercise to upper body (e.g. rowing); may be bilateral and affecting multiple costochondral areas; muscle groups may also be tender to palpation.	Simple analgesics; refrain from doing or reduce intensity of strenuous activities that provoke pain

CONCLUSION

Chest wall syndrome is the most common cause of chest pain admitted to the physician's office, in outpatient as well as in emergency departments, with a low morbidity and mortality rate. Diagnosis is established, particularly with specific anamnesis and physical examination. Pain sensations and high recurrency rates cause anxiety in some cases and lead to acute or chronic conditions. Because our understanding of this disease is still incomplete, more research and study are needed.

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