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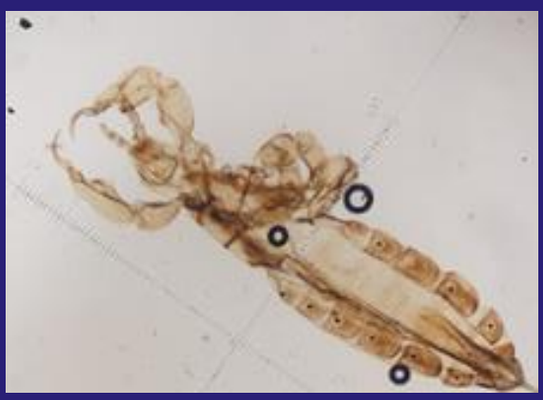

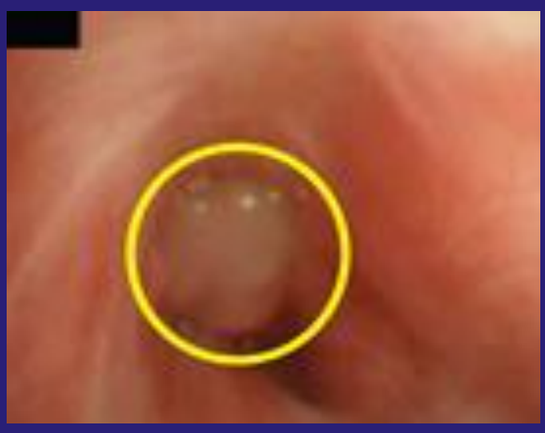

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Association between Hair Hygiene and *Pediculus capitis* Infestation among Elementary School Students in Sukorambi District, Jember Regency

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Abstract

Pediculus humanus capitis (*P.h. capitis*) is an ectoparasite which inhabits hair and scalp of human, causing a neglected disease called *Pediculus humanus capitis* infestation or *pediculosis capitis*. This disease, easily transmitted between people directly or indirect, often affects girls around 3–12 years old in tropical countries with high humidity. This can be avoided with applying personal hygiene focused on hair area (hair hygiene). Hair hygiene in this study was divided into several parameters, such as frequency of hair washing, shampoo usage, hair drying, towel sharing habit, comb and hair accessories sharing habit, head cover sharing habit, and close contact with an infested person. The aim of this study is not only to know the prevalence of *P. h. capitis* infestation, but also to determine the correlation between hair hygiene and *P. h. capitis* infestation among elementary school students in Sukorambi District, Jember Regency. This study was held around January to February 2024 using cross-sectional approach with total 83 respondents. Respondents were given several questions about parameters of hair hygiene and their hair was examined using lice comb to find *P. h. capitis*. Prevalence of *Pediculosis capitis* infestation among elementary school students in Sukorambi District reached 71.1%. Statistical analysis showed that towel sharing habit and comb and other hair accessories sharing habit had a significant relationship with *P. h. capitis* infestation (p-value <0.05). Multivariate analysis using logistic regression showed that comb and other hair accessories sharing habit were the most significant hair hygiene parameters.

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INTRODUCTION

Pediculus humanus capitis infestation or often known as *pediculosis capitis* is a neglected disease despite there being many cases globally.[12] It can affect every person but girls around 3-12 years old living in tropical country with high humidity are most likely affected more than boys, because they tend to get close to each other.[5,8] *P.h. capitis* is an obligate ectoparasite that inhabits scalp and hair, and sucks human blood to survive.[6,10] Its life cycle starts from eggs (nits), nymph, and then into fully developed adult lice that can get transmitted to people.[15]

P.h. capitis sucks human blood from people's head every three to six hours. It will trigger productivity of Ig-E. Histamin is released which will make human feels itchy[1] and develop anemia symptoms among people who are chronically infected. Other symptoms are feeling uncomfortable, losing concentration, and disturbed while studying and sleeping. Some people may develop secondary bacterial infection.[3,15,24]

About 6-12 million cases happen every year with prevalence rate reaching 50% in the US, United Kingdom, and France.[15] Some children got *P.h.capitis* infestation more than two times in Estonia[14]. Tropical Southeast Asia countries such as Malaysia, Philippines, and Thailand reached more than 60% in prevalence rate.[13,19,28] There were studies conducted in some cities in Indonesia about the prevalence of pediculosis capitis, which found most of them reached 50%.[16,20,27]

P.h. capitis infestation can be treated with topical drug with pediculicide effect, such as permethrin, topical ivermectin, and pyrethrin. There is also non-medical treatment such as removal of the lice, which is safer than medical treatment. Maintaining personal hygiene that focuses on hair and scalp area can be a way to prevent *P.h. capitis* infestation[15]. Hair hygiene is a way to keep hair cleanliness and health in order to prevent *P.h. capitis* infestation; it entails hair washing behavior, post hair washing, and avoid sharing hair accessories with others so it can prevent *P.h. capitis* infestation.[20,22]

There are not enough data and research studies about the prevalence rate of *P.h. capitis* infestation in Indonesia. Correlation between hair hygiene and *P. h. capitis* infestation has never been studied, especially in Sukorambi District, Jember Regency. Sukorambi District is one of the districts located in Jember Regency that has the largest population of children under 14 years old based on data by Badan Pusat Statistik (BPS) Jember. This research aimed to know the prevalence of *P. h. capitis* infestation and to find the correlation between hair hygiene and *P.h. capitis* infection among elementary school students.

MATERIALS AND METHODS

This is a cross-sectional study with purposive sampling technique. The research was held January-February 2024 in five elementary schools in Sukorambi District, Jember Regency. The respondents are elementary school girls who never been diagnosed with scalp diseases nor having treatment of *P.h. capitis* infestation. They had to be in fourth/fifth/sixth grade and their hair length must be under their shoulder when this research was conducted.

All respondents were given seven questions about their hair hygiene such as frequency of hair washing, shampoo usage, hair drying, towel sharing habit, comb and other hair accessories sharing habit, head cover sharing habit, also close contact with any infested person recently.

P.h. capitis infestation was examined using dry combing method throughout their hair; it was counted as a positive infestation if any lice or nits were found. Results from the questions and physical examination were analyzed using chi-square or Fisher's exact to determine the correlation between hair hygiene and *P.h. capitis* infestation. The most dominant hair hygiene parameter is determined using a logistic regression multivariate test.

RESULTS AND DISCUSSION

There are 83 respondents from five elementary schools. There are 59 (71.1%) respondents who tested positive in *P.h. capitis* infestation and 24 negative as the result of hair examination. The result counted as positive if there were found any egg lice (nits), nymph, or lice within hair and scalp area. Nits and lice found were identified using microscope to make sure it was *P.h. capitis*. Figure 1 shows an example of lice and nits that were found during this research using microscope with 40x magnification.

P.h. capitis were measured for their size, their length and width were about 2-2.5 mm and 0.5-1 mm. Lice eggs that found were 0.75-1 mm in length and 0.25-0.5 mm in width.

The questions that were given to the respondents are described in Table 1 below. Most respondents wash their hair at least three times per week, using shampoo, drying their hair, not sharing their towel and head cover, sharing their hair accessories, and also had close contact with an infested person.

Table 1. Distribution of hair hygiene parameters

Variable	Category	Total (n=83)	%
Frequency of hair washing	≥3x/week	62	74.7
	<3x/week	21	25.3
Shampoo usage	Yes	80	96.4
	No	3	3.6
Hair drying	Yes	53	63.9
	No	30	36.1
Towel sharing habit	Yes	37	44.6
	No	46	55.4
Comb and other accessories sharing habit	Yes	52	62.7
	No	31	37.3
Hair and head cover sharing habit	Yes	24	28.9
	No	59	71.1
Close contact with infested person	Yes	68	81.9
	No	15	18.1

There were seven parameters analyzed using SPSS to determine the correlation between the parameters and *P.h. capitis* infestation.

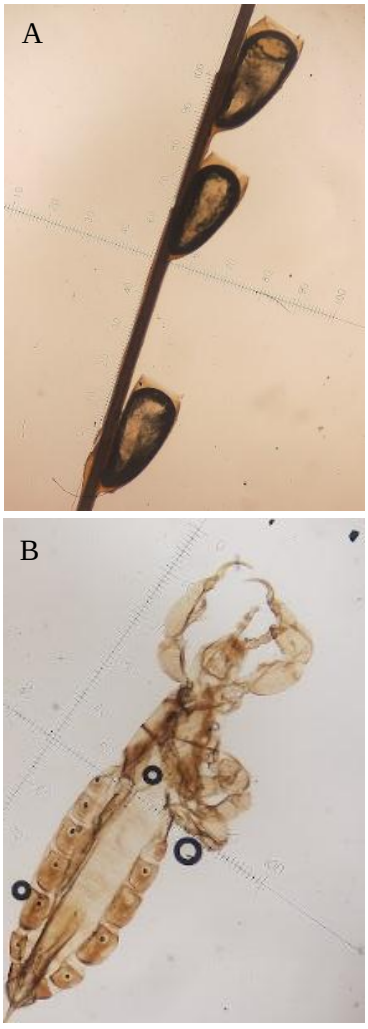

Figure 1. *P. h. capitis* with 40x magnification A) Lice eggs (nits) B) Mature head lice

Table 1. Hair washing frequency

Hair washing	Infestation (+)	Infestation (-)	p-value	OR
≥3x/week	41	21	0.087	0.325
<3x/week	18	3		

Table 2 shows there are 41 respondents washing their hair more than three times a week and 18 respondents washing their hair less than three times a week who got *P.h. capitis* infestation, meanwhile 21 respondents who wash their hair more than three times a week and three respondents washing their hair less than three times a week did not get *P.h. capitis* infestation. After being analyzed using chi-square test, it resulted in p-value 0.086 and OR 0.325. It means there is no significant relationship between hair washing frequency and *P.h. capitis* infestation (p-value >0.05); hair washing more than three times a week has risk of having *P.h. capitis* infestation 0.3 times more than washing hair less than three times a week.

No significance was found between hair washing frequency and *P.h. capitis* infestation in line with some previous studies.[18,21,27] This is because hair washing alone could not kill the lice. Hair washing is focused on cleaning up the hair scalp area and reducing hair moisture. The lice still can survive with a healthy environment. After hair washing, people should do manual hair examination to make sure there are no lice left. It will be more effective than just doing hair washing.[4,16,17]

Table 2. Shampoo usage

Shampoo usage	Infestation (+)	Infestation (-)	p-value	OR
Yes	57	23	1.000	-
No	2	1		

Table 3 shows 57 respondents washing their hair using shampoo and two respondents not using shampoo got *P.h. capitis* infestation, meanwhile 23 respondents who use shampoo and one respondent who did not use shampoo did not get *P. h. capitis* infestation. After being analyzed using Fisher's exact test, it resulted 1.000 in p-value. It means there was no significant relationship between shampoo usage and *P. h. capitis* infestation (p-value >0.05). No significance was found between shampoo usage and *P. h. capitis* infestation in line with previous studies.[16,18,20] Almost all shampoo products that are sold publicly do not contain pediculicide or substances that will kill *P. h. capitis*, it is only to clean, give moisture, and balance pH around the hair area.[15,22]

Table 3. Hair drying

Hair drying	Infestation (+)	Infestation (-)	p-value	OR
Yes	38	15	0.870	1.086
No	21	9		

Table 4 shows there were 38 respondents who dry their hair and 21 respondents who never dry their hair who got *P. h. capitis* infestation, meanwhile 15 respondents who dry their hair and nine respondents who never dry their hair did not get *P. h. capitis* infestation. After being analyzed using chi-square test, it resulted in p-value 0.870 and OR 1.086. It means there was no significant relationship between hair drying and *P. h. capitis* infestation (p-value >0.05); drying hair has risk of having *P. h. capitis* infestation one time more than not drying hair.

No significance between hair washing frequency and *P. h. capitis* infestation was the same result as a previous study.[11] This is because drying hair will not kill the lice.

Drying hair is a hair hygiene process that reduces hair moisture and humidity, it should be done with giving pediculicide to kill the lice. The lice still can survive with that environment if pediculicides are not used or being picked manually.[11,15]

Table 1. Towel sharing habit

Towel sharing habit	Infestation		p-value	OR
	(+)	(-)		
Yes	31	6	0.022	3.321
No	28	18		

Table 5 shows there were 31 respondents who share their towel and 28 respondents who never share their towel who got *P. h. capitis* infestation, meanwhile six respondents who share their towel and 18 respondents who never share their towel did not get *P. h. capitis* infestation. After being analyzed using chi-square test, it resulted in p-value 0.022 and OR 3.321. It means there was significant relationship between towel sharing habit and *P. h. capitis* infestation (p-value <0.05); towel sharing has three times greater risk of having *P. h. capitis* infestation than not sharing towel.

Significance between hair washing frequency and *P. h. capitis* infestation had the same result with some previous studies .[9,23,26] This is because towel sharing can trigger indirect *P. h. capitis* transmission between people. Lice could crawl within the towel and will stay there for hours until days and when someone uses the towel to rub their hair and scalp, they will get a new host to live on.[2,15]

Table 2. Comb and other hair accessories sharing habit

Comb and other hair accessories sharing habit	Infestation		p-value	OR
	(+)	(-)		
Yes	45	7	0.000	7.806
No	14	17		

Table 6 shows there were 45 respondents who share their comb also other hair accessories and 14 respondents who never share their comb and also other hair accessories who got *P. h. capitis* infestation, meanwhile seven respondents who share their comb also other hair accessories and 17 respondents who never share their comb or other hair accessories did not get *P. h. capitis* infestation. After being analyzed using chi-square test, it resulted in p-value 0.000 and OR 7.806. It means there was significant relationship between towel sharing habit and *P. h. capitis* infestation (p-value <0.05); comb and other hair accessories sharing has risk of having *P. h. capitis* infestation three times bigger than not sharing.

Significance between comb and other hair accessories sharing habit and *P. h. capitis* infestation had the same result with some previous studies.[9,16,23,26] Comb and other hair accessories sharing can trigger indirect *P. h. capitis* transmission between people. Lice could stay there for hours until days and when someone uses the comb or other hair accessories, they will get a new host to live on.[2,15]

Table 3. Head and hair cover sharing habit

Head and hair cover sharing habit	Infestation		p-value	OR
	(+)	(-)		
Yes	19	5	0.300	1.805
No	40	19		

Table 7 shows there were 19 respondents who share their head cover and 40 respondents who never share their head cover who got *P. h. capitis* infestation, meanwhile five respondents who share their head cover and 19 respondents who never share their head cover did not get *P. h. capitis* infestation. After being analyzed using chi-square test , it resulted in p-value

0.300 and OR 1.805 . It means there was no significant relationship between head or hair sharing habit and *P. h. capitis* infestation (p-value >0.05); head and hair cover sharing has a one time greater risk of having *P. h. capitis* infestation than not sharing.

No significance between hair or head cover sharing habit and *P. h. capitis* infestation was the same result with some previous studies.[21,27,29] Head cover such as veil, scarf, and mukena (prayer veil) mostly has soft and smooth surface so it will be difficult for lice to crawl there. Also, many people always use a kind of personal fabric to cover their hair before using veil or helmet. If their veil or helmet is borrowed, it will not cause any indirect transmission.[25]

Table 1. Close contact with infested person

Close contact with infested person	Infestation		p-value	OR
	(+)	(-)		
Yes	51	17	0.119	-
No	8	7		

Table 8 shows there were 51 respondents who had close contact with an infested person and eight respondents who did not have close contact with an infested person who got *P. h. capitis* infestation, meanwhile 17 respondents who had close contact with an infested person and seven respondent who did not have close contact with an infested person did not get *P. h. capitis* infestation. After being analyzed using Fisher's exact test, it resulted in p-value 0.119. It means there was no significant relationship between close contact with an infested person and *P. h. capitis* infestation (p-value >0.05). It was caused by there being no head to head interaction between two people that are close to each other, so the lice would not get transmitted because lice only can crawl, not fly or jump toward other people's hair.[7,20] Beside that, we did not know nor ask about preventive care that individuals already did to prevent head lice transmission.

Among seven parameters about hair hygiene, parameters that have p-value <0 are comb and other hair accessories sharing habit, and close contact with an infested person.

Table 2. Multivariate analysis

Variable	p-value	OR	CI 95%
Frequency of hair washing	0.176	0.351	0.077-1.601
Towel sharing habit	0.175	2,431	0.674-8.774
Comb and other hair accessories sharing habit	0.004	5,581	1,720-18,106
Close contact with infested person	0.558	1,552	0.357-6,753

Table 9 shows the result of multivariate analysis. Comb and other hair accessories sharing habit is the most dominant hair hygiene parameter that can cause *P. h. capitis* infestation with p-value 0.004, OR 5.581, and CI 95% in range 1,720-18,106. That habit can trigger indirect transmission of *P. h. capitis* to other individuals.

Hair hygiene is one of preventive care to prevent ourselves from getting *P. h. capitis* infestation. However, there are other ways to prevent the infestation. Also, curative care is needed because it can kill the lice more effective. Prevalence rate is still high among elementary school students, so health promotion needs to be done by the government.

STRENGTH AND LIMITATION

Few studies having discussed about this topic is the limitation of this study thus more research is needed. Also, the answers from respondents are mostly subjective, the authors did not ask to crosscheck respondents' answers. However, we believe this study will help other people to research more about this topic.

CONCLUSIONS

Prevalence rate of *P.h. capitis* infestation among elementary school students in Sukorambi District, Jember Regency was counted 71. There were two parameters which have a significant relationship with *P.h. capitis* infestation. The most dominant hair hygiene parameter toward *P.h. capitis* infestation is hair accessories sharing habit because this habit may trigger indirect transmission between people.

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ETHICAL CLEARANCE

The research protocol was approved by The Ethics Committee of the Faculty of Medicine, Jember University (0152/UN25.1. 10.2/KE/2024).

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest during this research.

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AUTHOR CONTRIBUTION

First author designed, collected, and analyzed the data. Second and third author contributed to data interpretation and manuscript writing. All authors reviewed and approved the final manuscript.

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In Vitro Analysis of SARS-CoV-2 Variants that Caused Severe COVID-19 in The Elderly

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the global problem of respiratory disease from 2019 to 2024. One of the earliest variations in the SARS-CoV-2 S protein was the S D614G mutation. SARS-CoV-2 has several important variants, namely, Alpha, Beta, Gamma, Delta, and Omicron. Omicron is the variant that has caused severe health problems, some resulting in death, in the elderly. Omicron has further differentiated to some well-known variants, such as BA.1, BA.2, BA.2.75, BA.5, BQ.1.1, and XBB.1. According to Japanese Government data, the number of citizens aged 65 years old and above reached 28.9% in 2021. From our previous experiment, antibodies of the elderly that have received four doses of mRNA vaccine still could not optimally neutralize Omicron BQ.1.1 and XBB.1. We aimed to analyze the plaque size of SARS-CoV-2 variants that caused severe COVID-19 in the elderly. SARS-CoV-2 variants were seeded in Vero E6-TMPRSS2 cell culture to create plaques. The resulting plaques were analyzed with ImageJ application to select solitary plaques and to determine plaque sizes. The size of BA.1 plaque was indifferent to BA.2 plaque. The plaque area comparison result was as follows: BA.1/BA.2<BA.5<BA.2.75<BQ.1.1<XBB.1. The plaque sizes of Omicron BQ.1.1 and XBB.1 were bigger than those of Omicron BA.1 and BA.2. The plaque sizes of all Omicron variants were smaller than those of the previous variants, S D614G and Delta. The result of this *in vitro* experiment inferred that there is increase in fusogenicity of BQ.1.1 and XBB.1, when compared with BA.1 and BA.2.

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INTRODUCTION

The etiological agent responsible for the coronavirus disease 2019 (COVID-19), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been widely known to have several variants. The original variant of SARS-CoV-2 that caused COVID-19 has been replaced by the S D614G variant, which was characterized by mutation in the gene encoding the S protein. The World Health Organization (WHO) reported five SARS-CoV-2 main variants that have distinctive differences compared to the original variant of SARS-CoV-2, including Alpha, Beta, Gamma, Delta, and Omicron.[1,2]

Omicron, the latest SARS-CoV-2 variant, caused milder symptoms compared to other previously detected variants. Omicron was also reported to have multiple mutations in the gene encoding the S protein, which increases the risk of SARS-CoV-2 reinfection after COVID-19 vaccination.[2]

Furthermore, Omicron has been observed to differentiate into several well-known variants, including BA.1, BA.2, BA.5, BQ.1.1, and XBB.1.[2] These variants have contributed to the abundance of COVID-19 cases worldwide. The abundant COVID-19 cases caused by Omicron did not escalate the concern because it has mild impacts on adults, but severe impacts leading to the risk of death usually occur in the elderly.[3,4]

Elderly is defined as people aged 65 years and above. Its population accounted for 28.9% of the population in 2021, according to the data from the Japanese government.[5] The immune response in the elderly gradually declines with time[4]. A previous study reported that the antibodies in elderly who had received four doses of the mRNA vaccine were still unable to optimally neutralize the BQ.1.1 and XBB.1 variants.[6]

We aim to investigate whether the increased severity of COVID-19 in the elderly was caused by the decrease of immunity or increase of virus pathogenicity. Here, we report an analysis of SARS-CoV-2 variants in cell cultures, including the BA.1, BA.2, BA.5, BA.2.75, BQ.1.1, XBB.1, S D614G, and Delta variants.

MATERIALS AND METHODS

This research was operated according to biosafety level 3 (BSL-3) protocols. Vero E6-TMPRSS2 cell was used because this cell line expresses the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease serine 2 (TMPRSS2), which could help the virus to enter the cell. In addition, the nature of these cells that adhere to the bottom of the well and are low in interferon production serve as advantages in this research, in which SARS-CoV-2 is a virus that is sensitive to interferons.[7]

SARS-CoV-2 variants were inoculated into Vero E6-TMPRSS2 cell cultures to compare the diameter of the plaques formed. Eight variants were used, i.e., Omicron BA.1, Omicron BA.2, Omicron BA.5, Omicron BA.2.75, Omicron BQ.1.1, Omicron XBB.1, S D614G, and Delta. The source and whole genome sequencing identification of variants had been documented in the Global Initiative on Sharing All Influenza Data (GISAID) database under identification number EPI_ISL_7418017, EPI_ISL_9595859, EPI_ISL_13241867, EPI_ISL_13969765, EPI_ISL_15579783, EPI_ISL_15669344, LC644163 (DNA Data Bank of Japan), and EPI_ISL_2158617, respectively. These viruses were subcultured from isolates from

COVID-19 patients with low passage numbers.

The infected cells were incubated for seven days in a medium containing methylcellulose. After incubation, cells were rinsed, fixed, and stained using the crystal violet dye.

Plaque is an empty and clear area (unstained) seen as a transparent dot. It is formed as the dead cells detach from the base due to the cytotoxic effects of the virus (Figure 1). All experiments were performed in duplicate to obtain consistent results.

Single plaques are considered as the result from infection by a single virus. The width of the plaque depends on the ability of the virus to disseminate from the first infected cell to nearby cells. The plaques were analyzed using the ImageJ application to select single plaques and determine the mean plaque size or diameter.

The plaque sizes were entered as data for statistical analyses. The statistical analyses were performed using one-way analysis of variance (ANOVA), followed by pair-wise comparisons with independent samples t-test to compare differences in plaque size between each group. Data were analyzed using SPSS Statistics 25.0.

RESULTS AND DISCUSSION

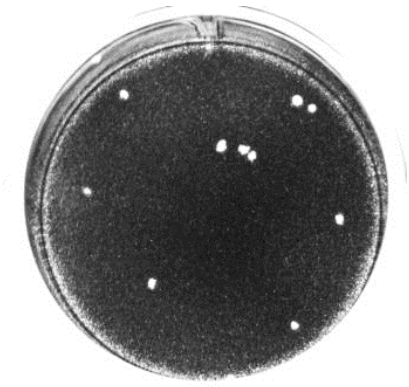

Figure 1. Crystal violet-stained plaque assay plate explains the cytopathic effect of the virus that formed clear plaques as transparent dots.

According to the analysis of 90 plaques from each variant, the mean plaque area were BA.1=BA.2<BA.5<BA.2.75<BQ.1.1<XBB.1. The plaque size of BA.1 were insignificantly different from the plaque size of BA.2. The plaque sizes of BQ.1.1 and XBB.1 were bigger that those of BA.1 and BA.2. However, the plaque area formed by several Omicron variants was still smaller when compared to S D614G and Delta variants. Table 1 shows the results of plaque size of SARS-CoV-2 variants on Vero E6-TMPRSS2 analyzed using ImageJ.

Table 1. Mean, median, and standard deviation of plaque size of SARS-CoV-2 variants on Vero E6-TMPRSS2

	Mean (mm^2)	Median (mm^2)	Standard Deviation
BA.1	0.106	0.107	0.035
BA.2	0.108	0.1	0.042
BA.5	0.163	0.16	0.026
BA.2.75	0.198	0.194	0.017
BQ.1.1	0.24	0.24	0.035
XBB.1	0.293	0.29	0.028
S D614G	0.308	0.305	0.03
Delta	0.384	0.388	0.053

One-way ANOVA statistical test revealed $p < 0.05$, indicating a difference between groups. The independent samples t-test showed that other than the plaque area of BA.1 and BA.2, there were significant differences between plaque area of the rest of the variants ($p < 0.05$). Figure 2 shows the plaque size comparisons of each SARS-CoV-2 variant, accompanied by the results of the two-tailed t-test analysis.

In a viscous media such as methylcellulose medium, SARS-CoV-2 infection relies on the fusogenicity of the virus, i.e., ability to form a membrane fusion between the infected and healthy cells. The fusion between cells causes the formation of syncytia, a multinuclear cell formed by multiple cell fusion.[8,9] The

formation of syncytia on S D614G and Delta variants could be observed two days after infection, while the syncytia on Omicron variants could be observed four days after infection. High fusogenicity and replication ability were found in the Delta variant of SARS-CoV-2, as revealed by the largest plaque size in this experiment. The association between the fusogenicity and SARS-CoV-2 pathogenicity remains unclear.

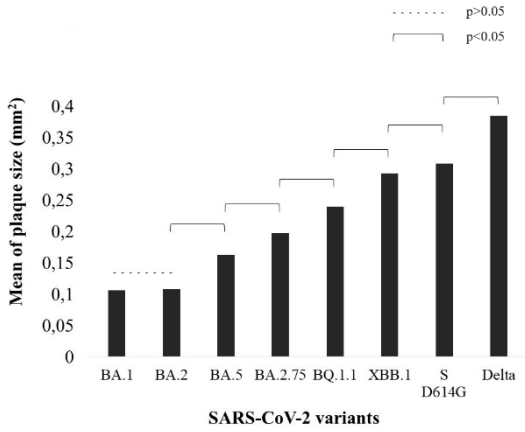

Figure 2. Plaque size comparisons of SARS-CoV-2 variants on Vero E6-TMPRSS2

It was initially thought that the fusogenicity of the virus was influenced by the P681 mutation in the gene encoding the S protein, a class I fusion glycoprotein that plays a role in the process of attachment and entry of the virus into cells. Moreover, it was discovered that the fusogenicity of the virus affects several factors, including the N-terminal domain and the cleavage process of the S protein, which results in the separation of the S1 and S2 regions in the S protein.[10,11] Mutations in certain regions of the S protein can also cause changes in the fusogenicity of the virus.[10-15]

Omicron has undergone major mutations in its genes, including the S protein-encoding gene. In the early generation of Omicron, BA.1 and BA.2, there was a decrease in the use of TMPRSS2 during the process of virus entering the cells through the membrane fusion. Instead, the virus enters cells through a process called endocytosis. This theory explains why the fusogenicity of Omicron variants, BA.1 and BA.2, was low.[16,17] These findings also support the results of this research, which showed that BA.1 and BA.2 formed the smallest plaque area compared to other variants.

This research also revealed a trend in plaque size of the newer generation of Omicron variants (BA.5, BA.2.75, BQ.1.1, and XBB.1.), in which the plaque size tends to be larger than the old generation of Omicron variants. Only the BQ.1.1 and XBB.1 variants were observed to have almost the same plaque size compared to the S D614G variant. These findings show that SARS-CoV-2 is still evolving to find its ideal design.

STRENGTH AND LIMITATION

The strength of this study is that it is an *in vitro* study, where the variables can be limited to minimum. The use of live virus from different variants, instead of recombinants[10,15,18-21], could show the real virus behavior.

The use of Vero E6-TMPRSS2 cells could be a limitation in this research. Vero cells are a lineage of cells isolated from kidney epithelial cells from an African green monkey, not a human.[22-25]

CONCLUSIONS

In vitro results in this research revealed an increase in the fusogenicity of the BQ.1 and XBB.1 compared to the BA.1 and BA.2 variants. Further studies need to be conducted to confirm these results with clinical findings *in vivo*.

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ETHICAL CLEARANCE

This research protocol was approved by the Ethical Committee of Kobe University Graduate School of Medicine (approval no. B200200) on 15 April, 2022.

CONFLICT OF INTEREST

The authors do not have conflict of interest.

AUTHOR CONTRIBUTION

SSu designed the experiment, drafted the manuscript, and revised the manuscript. SSu and LW did the experiment. SSu and CPT did the data analysis. CPT translated the manuscript. SSa provided consultations.

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Correlation between Complete Blood Count Parameters with Procalcitonin in Immunogenomic Phases of COVID-19 Patients

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Abstract

Coronavirus Disease 2019 (COVID-19), a global pandemic caused by SARS-CoV-2, presents varying degrees of severity influenced by different immunogenomic phase. The immunogenomic phase that occurs in patients with COVID-19 is divided into three phases, namely the initial phase, propagating phase, and complicating phase. Severity disease progression can be monitored from the results of complete blood count (CBC) parameters and several inflammatory parameters such as procalcitonin. The purpose of this study was to investigate, during the immunogenomic phase of COVID-19 patients, the correlation between PCT levels and full blood count parameters. Patients treated at Dr. Soetomo General Hospital for COVID-19 were the subjects of this cross-sectional study. Data analysis used in this study is Kolmogorov-Smirnov Test for normality, followed by Wilcoxon signed-rank test and bivariate Pearson correlation test to determine the correlation between complete blood count (CBC) parameters and PCT. Our findings reveal that most patients are male, predominantly aged between 50 and 60 years. Distinct variation of CBC parameters and PCT levels were observed in each phase. A significant relationship between these hematological markers, the immunogenomic phase and the progression of the disease. The PCT level of COVID-19 patients was associated with parameters of red blood cells, including hemoglobin, hematocrit, and the width-standard deviation of red blood cell distribution, leukocytes and their differential count, including lymphocytes and neutrophils, and platelets. This analysis further understanding regarding the hematological dynamics in COVID-19 patients, providing important information about the pathophysiology of the disease and potential biomarkers for monitoring its progression.

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INTRODUCTION

Wuhan City, Hubei Province, China, was the site of the 2019 Coronavirus Disease (COVID-19) outbreak in December. On March 11, 2020, Global Health Organization (WHO) officials announced the COVID-19 pandemic. This outbreak was initially linked to zoonotic transmission at a market, which subsequently spread rapidly in the community through human activities.[1] To date, COVID-19 is still attacking communities around the world.

The SARS-CoV-2 coronavirus is the one responsible for the COVID-19 pandemic. In mild instances, the illness manifests as a persistent cough and fever; in severe instances, it can progress to pneumonia or acute respiratory distress syndrome, both of which can be fatal. Severe acute infections of COVID-19 involve cytokine storms and hyperinflammation leading to much greater morbidity and death.[2] The disease progresses through three immunogenomic phases: the initial phase (mild or asymptomatic), the propagating phase (moderate to severe pneumonia within 7-14 days of infection), and the complicating phase (multiorgan failure after 14 days).[3]

When assessing the severity of COVID-19 and trying to figure out how afflicted people will fare, a standard full blood count is essential. Factors such as hemoglobin, WBC, and platelets are part of this. The ratio of neutrophils to lymphocytes (NLR) is an important indicator, as increased neutrophils indicate systemic inflammation, while decreased lymphocytes suggest sequestration at inflammation sites and apoptosis.[4] Serious cases of COVID-19 are associated with elevated levels of various other parameters, such as procalcitonin (PCT), C-Reactive Protein (CRP), d-dimer, ferritin, and many more.[4]

An increased risk of severe COVID-19 has been linked to higher levels of procalcitonin (PCT), according to some research.[5] Procalcitonin is crucial in COVID-19. Typically, PCT is elevated in bacterial infections; nevertheless, increased PCT levels in severe cases of COVID-19 may also suggest secondary bacterial infections or significant inflammation. Thus, PCT tend to rise progressively across the immunogenomic phases. Elevated PCT levels may reflect severe disease progression in COVID-19, helping diagnose bacterial co-infection in viral infections, particularly when severe symptoms arise during the complicating phase.[6] The increase in PCT can be explained by looking at its synthesis pathway, that are controlled by different cytokines, like IL-6 and TNF-a. As an abnormal immune response can initiate PCT production, hyperinflammation has been demonstrated to play a role in the progression of COVID-19 infections.[7,8] Nevertheless, there is a lack of research that connects PCT with full blood count parameters in COVID-19 patients, especially when it comes to the immunogenomic stages.

A correlation between PCT and full blood count parameters in Indonesian COVID-19 patients, particularly in Surabaya, has received little attention from researchers. In order to better diagnose and treat COVID-19 patients, this study intends to search for a connection between PCT and complete blood count parameters. Elevated PCT levels help guide antibiotic use by identifying bacterial co-infections in COVID-19 cases, supporting a more targeted approach to treatment. Effective antibiotic stewardship is essential to prevent misuse, particularly given that elevated PCT can guide appropriate antibiotic use, especially in bacterial co-

infections, thereby improve patient outcomes in bacterial complications associated with COVID-19. [9]

MATERIALS AND METHODS

Located in Surabaya, East Java, Indonesia from June 2020 through July 2021, participants with COVID-19 were enrolled in this study at Dr. Soetomo General Hospital. Information was culled from COVID-19 patients' medical records. Individuals who met the age requirement of ≥18 years and had a confirmed diagnosis of COVID-19 were considered for participation. The exclusion criteria encompassed patients with no complete medical record of complete blood count (CBC) parameters and procalcitonin. A minimum number of subjects was required for the sample selection, which included consecutive sampling. calculated using Cochran's formula for cross-sectional studies during 2022:

$$n = \frac{Z\alpha^2.p.q}{d^2}$$

Information:
n = number of samples
Z: *alpha risk expressed in z score*
p: *expected prevalence*
q: 1-p
d: *absolute precision* = 5%

An ethical committee at Surabaya's Dr. Soetomo General Hospital gave their stamp of approval to this research (Ref No. 0600/LOE/103.4.2/IX/2021). We gathered information from patients' medical records and routine laboratory complete blood parameters. This study examined variables such as PCT as a dependent variable and complete blood parameters as independent variables in a cohort of COVID-19 patients during the immunogenomic phase, which includes initial, propagating and complicating phase. Immunogenomic phases of patients was determined by an Internist with the criteria as described below. The initial phase of COVID-19 involves asymptomatic or presymptomatic cases and is frequently associated with moderate infections of the upper respiratory tract, including mild fever, dry cough, and sore throat, and malaise, without severe signs like dyspnea, or digestive symptoms, such as diarrhea, nausea and vomiting.

Proinflammatory chemokines and cytokines trigger neutrophil infiltration, worsening lung inflammation. Propagating phase was diagnosed when the infection affects lower airways and organs, with mild to severe pneumonia. Symptoms range from cough and mild breathlessness to severe respiratory distress and hypoxia. Lymphopenia and elevated fibrinogen levels are observed. Complicating phase was diagnosed when organ deteriorates, commonly affecting cardiovascular and kidney, with laboratory findings as severe lymphopenia, high neutrophil and leukocyte counts, and elevated D-dimer levels in non-surviving patients.

Laboratory Testing

Patients who were monitored for procalcitonin and who had their blood counts taken regularly were the ones whose records were used to compile all of the data. Arkan Medical of Indonesia provided the EDTA tubes used to draw blood samples from the veins. Complete blood count parameters and PCT were derived from routine hematology analyzer. Both complete blood count and PCT, samples were processed immediately using the Sysmex XN-1000 analyzer. The Sysmex XN-1000, which integrates impedance, hydrodynamic focusing, and fluorescent flow cytometry, enables comprehensive blood counts and cell differentials,

facilitating detailed PBMC analysis measurements, providing consistent and high-throughput data necessary. [10]

Centrifugation was used to separate RBCs, and density gradient centrifugation was employed to separate PBMCs, or peripheral blood mononuclear cells. Following isolation, PBMCs were washed and counted for further analysis. Hematology analyzer Sysmex XN-1000 (Sysmex Corporation, Japan) was employed for detailed immune cell profiling for precise quantification of neutrophils, lymphocytes, monocytes, and other leukocyte subsets. PCT were calculated by a chemiluminescent immunoassay (CLIA) in which analyzer introduces antibodies that specifically bind to PCT in the sample. This binding process often involves chemiluminescent or fluorescent markers that emit light. The intensity of the signal is compared to a calibration curve created from samples of known concentration, allowing the system to accurately report the exact level. [10]

Complete blood count parameters included in the analysis were Hemoglobin (Hb), hemocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCHC, WBC, RBC, RDW, NEUT, EOS, BASO, MONO, and LYMPH counts, with differential counts in percentage and absolute counts in numbers, PLT, PDV, NLR, and PLR are all components of the hemoglobin concentration mean. Both the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) were calculated by dividing the respective totals of neutrophils and lymphocytes, respectively.

Statistical Analysis

The main variables as well as the characteristic variables of the patients were subjected to statistical analyses. The study participants' descriptive characteristics were analyzed using demographic variables like age and gender, as well as immunogenomic phases such as initial, propagating, and complicating. Data analysis was done to correlate CBC parameters with PCT during the immunogenomic phase of COVID-19 patients. We ran the Shapiro-Wilk normalcy test to see how the data were distributed. In order to look for non-normal data, we used a non-parametric variant of the paired t-test called a Wilcoxon signed-rank test. To further evaluate the relationship between PCT and CBC parameters, the Pearson test was run. The SPSS software, version 25, was used for all statistical analysis. In order for a finding to be deemed statistically significant, the p-value must be less than 0.05.

RESULTS AND DISCUSSION

Patient Characteristics

Information was culled from Dr. Soetomo General Hospital's medical records of COVID-19 patients from June 2020 to July 2021. After collecting 477 samples, they were re-selected based on the criteria for inclusion and exclusion. There were 477 patients surveyed, but only 410 met all inclusion and exclusion criteria.

Sample details and distribution are displayed in Table 1 of the study. The sample consisted of more male COVID-19 patients than female patients in each phase. Males exhibited the highest prevalence of COVID-19 patients, according to other research. [11] These were then categorized into 410 samples in the initial phase, 276 samples in the propagating phase, and 119 samples in the complicating phase. These findings corroborate those of Garna et al. (2021), who found that most COVID-19 patients spend longer than seven days in the hospital, suggesting that most patients

have progressed beyond the acute phase of the disease.[12]

Table 1. Characteristics and distribution of samples in the study

Frequency (%)	Initial Phase (n=410)	Propagating Phase (n=276)	Complicating Phase (n=119)
Gender			
Male	229 (56)	156 (57)	65 (55)
Female	181 (44)	120 (43)	54 (45)
Age		**Mean ± SD**	
18 - 29	23.73 (7.07)	24.53 (5.65)	25.75 (0.7)
30 - 39	34.74 (6.36)	34.67 (6.36)	36.75 (4.24)
40 - 49	44.9 (6.36)	44.76 (6.36)	45.1 (6.36)
50 - 69	54.18 (6.36)	54.15 (6.36)	54.13 (6.36)
≥60	68.07 (19.79)	68.49 (19.79)	69.93 (19.79)

Characteristics of Complete Blood Count Parameters

Red blood cells, white blood cells, platelets, and other CBC parameters, NLR and PLR displayed in Table 2, based on the three immunogenomic phases. Normal ranges were based on the standard normal range provided by Sysmex XN-1000 derived from data analysis of healthy individuals, published guidelines from authoritative bodies like Clinical and Laboratory Standards Institute (CLSI).

As a screening tool for diagnostic evaluations and case monitoring, CBC parameters are assessments.[13] Studies have shown that CBC parameters, such as lymphocyte count, platelet count, NLR, have an important role in the management of COVID-19 patients as it can be used as a prognostic marker.[14]

Average hemoglobin, hematocrit, and RBC of COVID-19 patients in all three immunogenomic phases were below normal range. These findings corroborate those of Henry et al. (2020) and Palladino (2021) who found that patients with COVID-19 had lower hemoglobin levels and hematocrit concentrations, respectively. Studies have indicated that Covid patients are mostly anemic as it is the result of inflammation as a result of the spread of the COVID-19 virus.[14,15]

The red blood cell counts parameters analyzed in this study were MCV, MCH, MCHC, RDW-SD and RDW-SD. During the initial phase of the disease, all red blood cell count parameters were within the normal range. However, in the propagating phase, the average MCV and MCH values results were marginally lower than expected, whereas MCHC and RDW-CV were marginally higher than expected due to the invasion of the COVID-19 virus. Meanwhile, during the complicating phase, the average MCV and MCH values remained slightly lower than in the propagating phase, indicating a continued decline. Conversely, MCHC and RDW-CV values were slightly higher than the averages observed during the propagating phase, suggesting a trend toward increased variability in red blood cell size and concentration.

Previous studies have shown that MCV and MCH values tend individuals in the COVID-19 weight group to have substantially lower.[16] Another study reported higher MCHC levels in the propagating and complicating phases of the disease.[17] These changes in MCHC levels have been linked to lung function, oxygen demand, and COVID-19's total activity. Anemia is a known independent predictor of worsening disease outcomes in COVID-19 patients, and low MCHC levels are a common symptom of this condition. [17]

The study found that average leukocyte (WBC) counts were elevated above normal in both the initial and propagating phases of COVID-19, consistent with previous research that

Table 2. Characteristics of complete blood parameters

Parameters	Initial Phase (n=410)	Propagating Phase (n=276)	Complicating Phase (n=119)	Normal range
Hb	10.5 ± 1.7	9.45 ± 3	10.1 ± 2.4	11.0 – 16.6 g/dL
HCT	32.1 ± 5.4	28 ± 9.15	29.2 ± 5.5	35.2 – 52.1 %
MCV	92.5 ± 5.2	78.3 ± 3.85	82.75 ± 5.5	86.7 – 102.3 fL
MCH	30.3 ± 1.5	26.45 ± 1.35	28.45 ± 3.35	27.1 – 32.4 pg
MCHC	32.75 ± 0.25	33.8 ± 0.1	34.25 ± 1.75	29.7 – 33.1 g/dL
RBC	3.45 ± 0.39	3.575 ± 0.855	3.5 ± 0.43	3.69–5.46 $x10^6$ /µL
RDW-SD	45.3 ± 2.5	43.2 ± 4.25	45.3 ± 1.6	41.2 – 53.6 fL
RDW-CV	13.5 ± 1.6	15.1 ± 1.95	15.35 ± 1.35	12.2 – 14.8 %
WBC	11.29 ± 0.02	11.215 ± 3.57	9.48 ± 1.76	3.37 –10.0$x10^3$/ µL
NEUT%	85.9 ± 5.3	74.6 ± 5.15	61.75 ± 7.65	39.8 – 70.5 %
NEUT#	9.7 ± 0.62	8.255 ± 2.745	5.99 ± 1.81	0.00– 0.00$x10^3$/ µL
BASO%	0.25 ± 0.15	0.45 ± 0.05	0.9 ± 0.5	0.3 – 1.4 %
BASO#	0.025 ± 0.015	0.055 ± 0.02	0.075 ± 0.035	10^3 / µL
EOS%	0.75 ± 0.75	5 ± 2.75	5.25 ± 2.95	0.6 – 5.4 %
EOS#	0.085± 0.085	0.63 ± 0.48	0.445 ± 0.185	0.00–0.00$x10^3$/ µL
MONO%	6.95 ± 0.75	6.6 ± 2.4	8.05 ± 0.25	4.3 – 10.0 %
MONO#	0.785± 0.085	0.725 ± 0.065	0.76 ± 0.12	0.00–0.00$x10^3$/ µL
LYMPH%	6.15 ± 3.65	13.35 ± 5.45	24.05 ± 3.95	23.1 – 49.9 %
LYMPH#	0.695± 0.415	1.565 ± 0.275	2.21 ± 0.05	0.00–0.00 $x10^3$/ µL
IG%	2.85 ± 1.85	4.2 ± 1.2	0.7 ± 0.3	0.6 – 5.4 %
IG #	0.32 ± 0.21	0.46 ± 0.2	0.065 ± 0.015	10^3/ µL
PLT	198 ± 117	536.5 ± 87	305 ± 109	150 – 450x 10^6 /µL
PDW	11.05 ± 0.55	10.95 ± 0.35	12.15 ± 0.15	9.6 – 15.2 fL
MPV	10.6 ± 0.5	9.4 ± 0.25	11 ± 0.2	9.2 – 12.0 fL
NLR	1.079± 0.107	1.804 ± 0.004	1.104 ± 0.009	<5
PLR	9.574± 0.711	9.316 ± 0.22	9.959 ± 0.338	-

associates high leukocyte levels with severe cases of the disease.[18] The increase in leukocyte, known as leucocytosis, can be attributed to the severe condition experienced by hospitalized COVID-19 patients during the initial and propagating phase, meanwhile the improvement of leucocytosis was noted during the complicating phase.

Differential leukocyte counts revealed elevated neutrophil counts (neutrophilia) during the initial and propagating phases. Neutrophilia is a known marker of venous thrombosis and has likely contributed to inducing a necro-inflammatory response. Neutrophils also take advantage of neutrophil extracellular trap (NET) formation which promote collateral damage during viral infections. Improper NET production as a result of COVID-19 patients may cytokine storms that can become ARDS, SIRS, and

sepsis.[19] This increase in neutrophils is consistent with findings by Palladino (2021), who noted high neutrophil counts in COVID-19 patients seven to nine days after symptom onset. [20]

Lymphopenia, characterized by lower-than-normal lymphocyte counts, was observed in both the initial and propagating phases. This reduction is a well-documented hematological disorder in COVID-19, potentially caused by viral attachment, immune injury, or lymphocyte exudation into inflamed lung tissue.[20,21] Significant lymphopenia, often appearing 7-14 days after symptom onset, correlates with worsening clinical status as it is linked with increased inflammatory mediators and cytokine storms.[21] Thus, it is considered a biomarker of infection severity.[22]

Additionally, the study observed lower basophil levels during the initial phase, which aligns with findings in immunocompromised patients during early viral infections.[20] This decline in basophils further underscores COVID-19 early on in the course of the immune system's complicated reaction to the virus.

Elevated during the propagating phase, which typically phase occurs 7-14 days after hospitalization. This finding aligns with the study conducted by Lucijanic I., 2021 which noted thrombocytosis in COVID-19 patient, particularly among younger individuals and fewer comorbidity.[23] Patients with COVID-19 with significantly higher than normal platelet levels were found to have a longer average stay Elevated platelet levels during this phase may be linked to cytokine storms and have been associated with longer hospital stays. [21,24]

Presentation of PCT levels Based on the Immunogenomic Phase of COVID-19 Patients

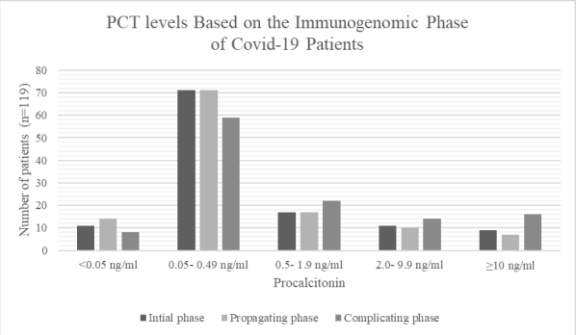

Figure 1. Characteristics of PCT based on immunogenic phase. < 0.5 ng/mL: not a systemic infection; 0.5 – 1.9 ng/mL: suspected sepsis; > 2.0– 9.9 ng/mL: severe sepsis; ≥10 ng/mL: severe bacterial sepsis or septic shock.

Only 119 COVID-19 patients were followed through the initial, propagating, and complicating phases (Figure 1). Consequently, all subsequent statistical analyses, including comparisons and correlations, will be conducted using this sample size. As the research indicated most COVID-19 patients had procalcitonin (PCT) levels in the range of 0.05-0.49 ng/mL across all immunogenomic phases. This proves that the majority of sufferers experience signs of infection. The results obtained aligns with the study conducted by Tong-Minh et al., 2022 it found that serious cases of COVID-19 and bacteria are frequently accompanied by elevated PCT levels. In a study conducted by Heer et al. (2021), it was found that patients infected with COVID-19 who were ventilator-dependent had elevated PCT levels.[26]

Table 3. Comparison of complete blood parameters with PCT based on immunogenic phase

	Initial Phase (n=119)	**Propagating Phase (n=119)**	**Complicating Phase (n=119)**
PCT	2.15 ± 6.8	2.36 ± 9.76	10.68 ± 35.34

During the initial phase and propagating phase PCT levels were in the rage of 2.0 – <10 ng/mL (Table 3) which indicate an ongoing severe sepsis. However, during the complicating phase, PCT levels were > 10 ng/mL which indicate critically ill with bacteria-related sepsis or shock. Typically, COVID-19 patients present low PCT levels upon hospital admission. However, these levels often rise within a few days as the disease progresses.

The increase in PCT that occurs in COVID-19 patients indicates that there is a bacterial co-infection.[27] Elevated PCT is particularly concerning as it may indicate the development of COVID-related pneumonitis with a complex pathophysiology involving endothelial dysfunction. Having elevated PCT levels almost quadruples the risk of developing a life-threatening infection.[21] These results emphasize how crucial it is to monitoring PCT levels used to assess the severity of the infection in patients with COVID-19.

Comparison of Complete Blood Count Parameters with Procalcitonin in the Immunogenomic Phase of COVID-19 Patients

In the initial phase, all parameters were not normally distributed except for HCT, MPV and PLR (Table 4). Meanwhile all parameters were not normally distributed except for Hb, HCT and MPV for propagating and complicating phases.

Table 4. Comparison of complete blood parameters with PCT based on immunogenic phase

PCT-CBC Parameters	Initial Phase (n=119)		Propagating Phase (n=119)		Complicating Phase (n=119)	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value
Hb (g/dL)	10.8 ± 2.9	<0.001*	11.0 ±2.7	<0.001*	10.6 ±2.5	<0.001*
HCT (%)	32.7 ± 8.8	<0.001*	33.3±8.4	<0.001*	32.0 ±7.6	<0.001*
MCV (fL)	85.4 ± 11.9	<0.001*	86.6 ±6.6	<0.001*	87.3± 6.7	<0.001*
MCH (pg)	28.6 ± 3.0	<0.001*	28.6 ±2.7	<0.001*	28.6± 2.4	<0.001*
MCHC (g/dL)	33.0 ± 1.6	<0.001*	33.1 ±1.6	<0.001*	32.8± 1.3	<0.001*
RBC (10^6 /µL)	4.0 ± 2.6	<0.001*	4.2 ±3.6	<0.001*	3.7± 0.9	<0.001*
RDW-SD (fL)	44.5 ± 6.9	<0.001*	46.1±8.7	<0.001*	48.0 ±8.7	<0.001*
RDW-CV (%)	14.4 ± 2.7	<0.001*	16.0 ±12.6	<0.001*	15.7 ±3.7	<0.001*
WBC (10^3/µL)	11.2 ± 7.3	<0.001*	13.5 ±8.2	<0.001*	12.0± 8.1	<0.001*
NEUT%	79.3 ± 13.8	<0.001*	78.4 ±13.8	<0.001*	73.4± 14.7	<0.001*
NEUT# (10^3/µL)	9.2 ± 6.8	<0.001*	11.3 ±8.0	<0.001*	9.5± 8.1	<0.001*
BASO%	0.280± 0.215	<0.001*	0.380 ±0.310	0.367	0.429± 0.307	0.012
BASO# (10^3/µL)	0.033± 0.036	<0.001*	0.046 ±0.047	<0.001*	0.043± 0.028	<0.001*
EOS%	0.840± 1.219	0.756	1.4 ±2.1	<0.001*	2.4± 2.5	0.038
EOS# (10^3/µL)	0.085± 0.138	<0.001*	0.122 ±0.176	<0.001*	0.213± 0.279	<0.001*
MONO%	7.5 ± 9.9	<0.001*	7.4 ±5.2	<0.001*	8.1± 4.9	<0.001*
MONO# (10^3/µL)	0.780± 1.367	0.357	0.838 ±0.441	<0.001*	0.817± 0.422	0.797
LYMPH%	12.1 ± 8.5	<0.001*	12.3 ±10.1	<0.001*	15.0± 9.7	<0.001*
LYMPH# (10^3/µL)	1.1± 0.6	<0.001*	1.2 ±0.734	<0.001*	1.4± 0.8	0.143
PLT (10^6 /µL)	316 ± 192	<0.001*	339.4 ±180	<0.001*	276.5± 157	<0.001*
PDW (fL)	11.17 ± 1.8	<0.001*	11.2 ±2.0	<0.001*	11.2± 2.4	<0.001*
MPV (fL)	10.6 ± 0.5	<0.001*	10.2 ±0.9	<0.001*	10.2± 1.0	<0.001*
NLR	1.079± 0.107	<0.001*	1.1 ±0.1	<0.001*	1.1± 0.1	0.239
PLR	9.57± 0.711	<0.001*	9.4 ±0.6	<0.001*	9.4± 0.6	<0.001*

*p-value <0.05; p-value were derived from Asymp. Sig. 2-tailed

During the initial phase, p-value for the variables in this study was <0.001 which indicates that the results were noticeably different. Except, the p-value between procalcitonin and percentage eosinophils and absolute monocytes was 0.756 and 0.357, respectively. Thus, indicating no significant difference between PCT and percentage eosinophils and absolute monocytes.

During the propagating phase, p-value for the variables in this study was <0.001, again indicating a significant difference in outcomes. However, the p-value between procalcitonin and percentage basophils was 0.367. Thus, indicating no significant difference between PCT and percentage basophils.

During the complicating phase, p-value for the variables in this study was <0.001, showing a significant difference in outcomes. However, the p-value between procalcitonin and absolute monocytes was 0.797, between procalcitonin and absolute lymphocytes was 0.143, between procalcitonin and NLR was 0.239, and between procalcitonin, all indicating no significant difference in outcomes.

From this study, complete blood parameters were significantly different when compared to PCT levels in each immunogenomic phase. However, several complete blood parameters were insignificant at different immunogenomic phase, such as percentage eosinophils and absolute monocytes, percentage eosinophils and absolute monocytes, absolute lymphocytes percentage and NLR.

Correlation of Complete Blood Parameters with Procalcitonin in the Immunogenomic Phase of COVID-19 Patients

Table 5. Correlation of complete blood parameters and PCT during the immunogenic phase

PCT-CBC Parameters	Pearson Correlation	Sig. (2-tailed)
Hb	-0.143**	**0.007***
HCT	-0.194**	**0.000****
MCV	-0.029	0.581
MCH	-0.022	0.673
MCHC	0.046	0.385
RBC	-0.079	0.137
RDW-SD	0.049	0.354
RDW-CV	0.007	0.891
WBC	0.154**	**0.004****
NEUT%	0.154**	**0.004****
NEUT#	0.168**	**0.001****
EOS%	-0.101	0.058
EOS#	-0.071	0.179
BASO%	-0.084	0.112
BASO#	-0.006	0.908
MONO%	-0.060	0.255
MONO#	0.005	0.924
LYMPH%	-0.157**	**0.003****
LYMPH#	-0.093	0.078
IG%	0.058	0.280
IG #	0.080	0.134
PLT	-0.118*	**0.026***
PDW	0.061	0.252
MPV	0.098	0.065
NLR	0.025	0.638
PLR	0.091	0.086

* Significant correlation at level 0.05 (2-tailed);
** Significant correlation at level 0.01 (2-tailed).

A bivariate correlation analysis was conducted to examine the relationship between complete blood parameters and procalcitonin levels across the immunogenomic phases of COVID-19, using the Pearson correlation method. The analysis, as detailed in Table 5, revealed a moderate yet significant positive correlation (p-value < 0.05) between procalcitonin and several key blood parameters, including hemoglobin (Hb), hematocrit (HCT), red cell distribution width-standard deviation (RDW-SD), white blood cell count (WBC), neutrophil percentages and counts (neutrophils% and neutrophils#), lymphocyte percentages (lymphocytes%),

and platelet count (PLT). These findings suggest a meaningful relationship between procalcitonin and these hematological markers, which may reflect the inflammatory and immune responses in COVID-19 patients during different phases of the disease.

These results highlight the complexity of the immune response in COVID-19, where certain blood parameters are closely linked with procalcitonin levels, while others show weaker or non-significant correlations. The significant correlations between PCT and WBC, neutrophil percentage and counts, and platelets align with the understanding that these markers are central to the body's response to infection. Neutrophilia, or elevated neutrophil counts, is a hallmark of severe inflammation and is often observed in COVID-19 patients, particularly during the propagating phase of the disease. IgG levels also usually increase after a long period of infection and the levels will decrease in patients with critical conditions compared to severe and mild conditions.[28] Meanwhile, eosinophils has an insignificant relationship between PCT as eosinophils are considered end-effector cells related to helminth infections, allergic inflammation, and causes of tissue damage.[29]

Meanwhile, moderate correlations between PCT and tests for hemoglobin, hematocrit, and the width-standard deviation of the red blood cell distribution suggest that these parameters are also influenced by the inflammatory milieu in COVID-19. Researchers found a correlation between the number of red blood cells in a patient's blood and the severity of their COVID-19 symptoms.[30,31] This is also supported by data obtained from this study that in all three phases of the immunogenomic, erythrocyte levels are less than normal which indicates the occurrence of anemia. Anemia, often characterized by low Hb and HCT levels, can be a consequence of chronic inflammation, while an increased RDW-SD reflects heterogeneity in red blood cell size, which may be linked to the stress response during infection. The association of these parameters with PCT indicates that they may serve as indirect markers of disease severity, particularly in the context of systemic inflammation.

Elevated PCT levels, along with changes in WBC, neutrophils, and platelets, suggest a robust inflammatory response that could be predictive of disease severity. The findings underscore the importance of a comprehensive approach to understanding the interactions between various hematological markers and procalcitonin during the different stages of COVID-19, which could provide insights into disease progression and severity.

STRENGTH AND LIMITATION

What made this research stand out was observed correlations between PCT, and various blood parameters provide insights into the mechanisms of disease progression in COVID-19. Due to its retrospective character, this study had certain limitations.

Many of the COVID-19 patients did not pass through all the immunogenomic phase. To confirm these results and investigate the possible causal links between these variables, future research should use longitudinal designs and larger samples and disease outcomes. Additionally, investigating the role of other biomarkers and their interactions with PCT could further enhance our understanding of COVID-19 pathophysiology.

CONCLUSIONS

This study provides a comprehensive analysis of COVID-19 patients based on various hematological parameters across different immunogenomic phases of the disease. The findings reveal significant differences in complete blood count parameters with PCT levels in each phase of the immunogenomic progression of the disease. Additionally, distinct variation in PCT levels was observed in each phase, indicating a significant relationship between these hematological markers and the immunogenomic phase or the progression of the disease. Hemoglobin, hematocrit, and the width-standard deviation of the red blood cell dispersal are some features of red blood cells, leukocytes and its differential count, such as neutrophils and lymphocytes as well as platelets were correlated with PCT level of COVID-19 patients. This analysis enhances our understanding of the hematological dynamics in COVID-19 patientsmaking important contributions to our understanding of the pathophysiology of the disease or potential biomarkers for monitoring its progression.

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ETHICAL CLEARANCE

With reference number 0600/LOE/103.4.2/IX/2021, the Ethical Committee of Dr. Soetomo General Hospital in Surabaya gave their approval to the study protocol.

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CONFLICT OF INTEREST

No conflicts of interest have been identified by the writers.

AUTHOR CONTRIBUTION

Every writer has made contributions to this work, we affirm. Every author has contributed to the initial draft and has made significant edits to improve it. With this work, all authors have signed off and taken responsibility.

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Scientific Journal of Tropical and Infectious Disease

Fungemia in Tertiary Hospitals; An Overview Fungal Profile, Antifungal Resistance, and Antifungal Therapy

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Abstract

Fungemia is a bloodstream infection caused by fungal pathogen and commonly occurs in hospitalized patients with certain risk factors. Indonesia itself is a tropical country with middle income that makes the incidence rate of fungemia tend to be higher, namely10/10,000 people. A recent study about candidemia conducted in Dr. Soetomo General Academic Hospital stated that the most common species that caused candidemia is Candida albicans (33.96%) and the blood sample mostly collected from patients from high care unit and patient with diabetes. We conducted this study to provide a new overview of data on the profile of the causes of fungal infections, patterns of fungal resistance to antifungals, and antifungal therapy in patients with fungemia in hospitalized patients at Dr. Soetomo General Academic Hospital, Surabaya, for the period of January - December 2023. This research is a descriptive study using the patient's medical records. Variables observed in this study include; gender, age, care unit, risk factor, species distribution, resistance pattern, type of antifungal therapy, and duration of antifungal therapy. Mostly the blood cultures are collected from female patients aged 0-9 years old. This study also found that most blood cultures are collected from patients in intensive care unit with use of CVC. Most of the patients did not receive antifungal therapy The most frequent found species is *Candida parapsilosis* with the highest resistance rate found in Amphotericin-B. The most common antifungal that is used is fluconazole which is mostly given within the range of 8-14 days .

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INTRODUCTION

Fungemia is a bloodstream infection caused by fungal pathogen and commonly occurs in hospitalized patients with certain risk factor[1,2]. Fungal pathogen can be divided into two categories; opportunistic and endemic agent which is influenced by geographic factors.[2] Fungemia is one of the problems in intensive care units especially in developing and middle income countries.[1] In Indonesia, the current data of incidence rate of candidemia is 10/10,000 with 30% mortality rate.[3] According to previous study about candidemia in Dr. Soetomo General Academic Hospital, the most common species that caused candidemia is *Candida albicans* (33,96%) and mostly the blood cultures are collected from intensive care units with the most common risk factors being CVC use and patients with diabetes mellitus.[4]

Until now, the gold standard method to diagnose fungemia is blood culture with macroscopic and microscopic examination for antifungal susceptibility test[5] Based on other study, increased number of mortality rate in fungemia patient with high risk factor is caused by fungal resistance; furthermore, it is important to discuss about resistance rate of fungal agents.[6,7]

Research about fungemia has rarely been done in developing countries, especially in Indonesia, although the incidence rate tends to be higher in developing countries. Dr. Soetomo General Academic Hospital itself is a tertiary hospital with many inpatient cases that require intensive care; however, until now there has not been found any study about species distribution of fungemia patients, patterns of fungal resistance, and therapy of fungemia patients. Therefore it is hoped that this study will provide the latest information to improve the management of patients' treatment and reference for study related to fungal bloodstream infection in the future.

MATERIALS AND METHODS

Population and Sample

The data used in this research were secondary data from medical records of inpatients with fungemia in Dr. Soetomo General Academic Hospital from January 2023 until December 2023. The sample used in this research is all medical records that contain patient's demographic data, inpatient unit, risk factor, antifungal sensitivity test results, antifungal therapy and the duration of antifungal therapy use. The total number of fungemia inpatients is 146 and the number of patients that meet all the criteria is 125 patients.

Methods

This research design is an observational study with retrospective approach to observe profile of fungemia inpatients in RSUD Dr. Soetomo within January – December 2023.

RESULTS AND DISCUSSION

The research results showed that the majority of fungemia inpatients is within the children age group between 0 – 9 years old, especially in <0 years old. This finding is similar to previous study about candidemia in Dr. Soetomo General Academic Hospital which stated that the highest incidence rate of candidemia occurred in the age group <0 years old.[4] In patients in the age group age <1 years old the immune system has not fully developed which causes them to be more susceptible to fungal pathogen.[6] A common immunological that effectively kills fungal pathogen is Th1 or Th17 immune response which only develops at early childhood stage > 1 year old.[8] As

shown in Table 1, there are not significant differences between number of male and female fungemia inpatients, which is relevant to previous study that stated gender is not the main risk factor in fungemia.[4,1] The majority of the blood cultures are isolated from the patients in ICU followed by patients in HCU. This study has similar results to other study that fungemia is more common among ICU patients due to many invasive procedures that tend to be occurred in ICU.[9,10] Fungemia tends to be an opportunistic infection which mainly infects individuals with risk factors.[11] In this study, most of the patients had several risk factors. Table 1 shows that in this research the most common risk factor is CVC usage. This result is similar to previous study that CVC usage is a common risk factor in fungemia patients due to catheters used are contaminated with fungal pathogens.[4,12]

Table 1. Characteristics of fungemia inpatients in Dr. Soetomo Surabaya General Academic Hospital, January 2023 – December 2023

Predictor	Amount	Percentage
Age		
0 – 9 years old	66	52.80
10 – 19 years old	9	7.20
20 – 29 years old	3	2.40
30 – 39 years old	9	7.20
40 – 49 years old	9	7.20
50 – 59 years old	15	12.00
>59 years old	14	11.20
Gender		
Male	62	49.60
Female	63	50.40
Medical Units		
Intensive care unit	33	26.40
High care unit	30	24.00
Pediatric wards	15	12.00
Medical wards	13	10.40
Neonatal intensive care unit	13	10.40
Surgery wards	9	7.20
Neonatal high care unit	6	4.80
Isolation wards	4	3.20
Pediatric intensive care unit	1	0.80
Pediatric high care unit	1	0.80

Risk Factor	Frequency n(%), n=125
CVC	44.00%
TPN	40.00%
Surgery	38.40%
Use of broad spectrum antibiotics > 14 days	24.80%
Preterm infants	21.60%
Patient with diabetes mellitus	13.60%
CKD	9.60%
Malignancy	7.20%
Immunocompromised	4.80%

Based on Table 2, the blood culture results from fungemia inpatient in 2023 found 125 fungal isolates with 15 species. The species that is commonly found in the blood culture is *Candida parapsilosis* (40.0%) followed by *Candida tropicalis* (20.00%) and *Candida glabarata* (12.00%). The results about species distribution on this study is not common, because several other studies had the result that the common cause of fungemia is *Candida albicans* which is believed to be caused by the azole antifungal used was not very common at that time.[13,4] However, currently, use of azole antifungals as therapy is very common which leads to decreased incidence of *Candida albicans* fungemia.[14] However this has caused an increasing incident of Candida non-albicans caused by Candida non-albicans resistance to azole antifungals.[14] A study having a similar result to this study was conducted in Japan that showed *Candida parapsilosis* being the most common species found in fungemia patients.[15] This is believed caused by use of echinocandins as antifungal treatment which is not relevant with this study because only two patients received echinocandin as antifungal theraphy.[15]

Improper use of antifungal treatment could lead to fungal resistance which has many predisposing factors that can lead to antifungal resistance.[16] Antifungal resistance mechanism in Candida species includes gene mutation, efflux pump overexpression, and biofilm formation.[17] Another study stated the incidence rates of fungemia caused by *Candida parapsilosis* have increased over the last two decades due to nosocomial transmission from prolonged use of medical devices such as Central Venous Catheter (CVC) and Top Parenteral Nutrition (TPN).[1418] Another study stated that *Candida parapsilosis* has ability to form biofilm on Central Venous Catheter or other prosthetic material and ability to grow in Top Parenteral Nutrition solutions, by which it can be concluded that *Candida parapsilosis* blood stream infections (BSI) are related to the exogenous route of fungal infection, which is relevant to this study.[19] In this study, *Candida tropicalis* is the most common fungal pathogen found in the patient's blood culture after *Candida parapsilosis*. Several studies conducted in tropical countries concluded that fungemia caused by *Candida tropicalis* commonly occurred in tropical countries such as Latin America and Asia.[20,21] Several studies stated that the decreased incidence of fungemia caused by *Candida albicans* is believed due to increased use of azole antifungals each year while the resistance rate of azole in *Candida albicans* species tends to be lower, which causes the change of incidence rate between fungemia caused by *Candida albicans* and *Candida non-albicans* each year.[22,4]

Table 2. Fungal species distribution from fungemia inpatients in Dr. Soetomo Surabaya General Hospital, January 2023 – December 2023

Species	Frequency	Percentage
Candida non-albicans		
Candida parapsilosis	51	40.80%
Candida tropicalis	26	20.80%
Candida glabarata	15	12.00%
Candida haemulonii var vulnera	5	4.00%
Candida haemulonii	4	3.20%
Candida duobushaemulonii	3	2.40%
Candida dubliniensis	1	0.80%
Candida guilliermondii	1	0.80%
Candida krusei	1	0.80%
Candida lusitaniae	1	0.80%
Candida rugosa	1	0.80%
Candida utilis	1	0.80%
Candida albicans	11	8.80%
Cryptococcus neoformans	2	1.60%
Kodamaea ohmeri	2	1.60%

Antifungal that is used for therapy is one of the main factors for successful therapy in fungemia patients; therefore, the patients that show symptoms of fungemia have to do a blood culture test to check whether there is an fungal pathogen and its sensitivity pattern.[1] As shown in Table 3, there are found several isolates that are resistant to Amphotericin-B, Micafungin, and Caspofungin which tends to be different from other study. Other study stated that fungal pathogens are commonly susceptible to echinocandin and polyene.[23] However, there is a study that has similar results by which Amphotericin-B has a high resistance rate especially in *Candida non-albicans* isolate.[24] Fungal resistance to Amphotericin-B is associated with ERG-3 gene mutation while fungal resistance to Micafungin and Caspofungin is linked to mutation in units FKS1 and FKS2.[2526] Furthermore, in this study there are found several isolates from *Candida non-albicans* that are resistant to azole antifungals such as Fluconazole and Voriconazole. Several studies stated that resistance to azole antifungals are commonly occurred in *Candida non-*

albicans isolate especially in *Candida glabarata* which is linked with mutation in ERG-11 gene.[27,23,28] Therefore, in this research it can be concluded that the most frequent found species is *Candida parapsilosis* with highest resistance rate found in Amphotericin-B. In several studies it is stated that there is found a significant degree of resistance rate of Amphotericin-B in *Candida parapsilosis* isolates.[29]

Table 3. Resistance rate to antifungal of fungemia inpatients in Dr. Soetomo Surabaya General Hospital, January 2023 – December 2023

Species (Frequency)	Antifungal (Isolates)	Resistance (%)
Candida albicans **(11)**	Amphotericin-B (11)	9.09
	Micafungin (11)	9.09
Candida non-albicans **(110)**	Fluconazole (88)	1.14
	Voriconazole (102)	1.96
	Caspofungin (83)	4.82
	Amphotericin-B (105)	11.3
	Flucytosin (107)	0.93
	Micafungin (93)	1.08

As shown in Table 4, 52% patients having fungal pathogen from the blood culture test were not treated with antifungal treatment, which is relevant to the Infectious Disease Society of America (IDSA) guideline that stated antifungal treatment should be given to patients tested positive for fungal pathogen in blood culture and having symptoms of infections such as fever.[30] This study further shows that the outcomes of the patient given antifungal treatment is that 56% of the patients are discharged. However, a successful therapy involves many other factors such as risk factors and duration of the treatment.[9] Based on Table 5, most of the patients that met the criteria to receive antifungal treatment were given fluconazole, which is similar to a study conducted in Tehran.[13] It occurs because Fluconazole is a broadspectrum antifungal and has several mechanisms of action such as overexpression of ERG-11 gene which is caused by the existence of Upc2 transcription factor and mutation of ERG-3 gene which cause thinning of the ergosterol wall.[31,28] In this study, it was also found that antifungal treatment is mostly given within the range of 8-14 days; however, several patients were discharges and there was not found a continuation of antifungal treatment.

Table 4. Antifungal therapy of fungemia inpatients in Dr. Soetomo Surabaya General Academic Hospital, January 2023 – December 2023

	Frequency	Percentage
Treated with antifungal	60	48%
Not treated with antifungal	65	52%

Table 5. Antifungal therapy and duration of antifungal therapy given to fungemia inpatients in Dr. Soetomo Surabaya General Academic Hospital, January 2023 – December 2023

	Frequency (%) n=60
Antifungal	
Fluconazole	58 (96.67%)
Micafungin	2 (3.33%)
Duration	
1-7 days	58 (96.67%)
8-14 days	2 (3.33%)
15-21 days	58 (96.67%)
22-28 days	2 (3.33%)
29-35 days	58 (96.67%)

STRENGTH AND LIMITATION

The strength of this study is there are not many studies about fungemia, especially in Indonesia, even though the incidence rates are high among ICU patients.

However, the limitations of this study were due to incomplete medical records especially on the duration of antifungal treatment, which caused inadequate data of duration of antifungal therapy.

CONCLUSIONS

This study shed light on the species distribution, patterns of antifungal resistance, and therapy of fungemia patients in Dr. Soetomo General Academic Hospital, Indonesia. The most frequent found species is *Candida parapsilosis* with highest resistance rate found in Amphotericin-B. Most of the patients did not receive antifungal therapy. Early detection and proper treatment is important for successful treatment of fungemia patients. This study highlights the importance of giving proper treatment to increase successful rate of treatment and decrease the risk of antifungal resistance of fungemia patients.

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ETHICAL CLEARANCE

The use of medical records for the data in this research is approved by the ethics committee of Dr. Soetomo Surabaya General Academic Hospital (1691/LOE/301.4.2/VI/2024).

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CONFLICT OF INTEREST

All of the authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Every author in this study equally contributed from the design to the implementation of the research, result analysis, and writing the manuscript.

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Article Review

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Diagnosis Approach of Endobronchial Tuberculosis: Literature Review

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Abstract

Pulmonary tuberculosis (PTB) remains a global health problem and the leading cause of death from infectious diseases. Indonesia as an endemic country and the second highest contributor of PTB cases in the world provides support and attention to PTB case finding and treatment success. Endobronchial tuberculosis (EBTB) is problematic PTB because the lesions are often not detected by sputum examination and chest X-ray. Clinically, there is no significant difference in symptoms between TB and EBTB. In general, EBTB gives a more severe clinical appearance due to airway stenosis. Bronchoscopy and thoracic computed tomography scan (CT scan), along with microbiological investigations, are the most useful diagnostic tools for confirming and evaluating tracheobronchial stenosis. In addition, bronchoscopy can also be used as a long-term treatment in cases of EBTB due to airway stenosis. The goals of treatment are the eradication of *Mycobacterium tuberculosis* (Mtb) bacilli with antituberculosis drugs (ATD) and the prevention of airway stenosis. Intervention of bronchoscopic techniques and surgery are required for those patients who develop severe tracheobronchial stenosis that causes significant symptoms, including dyspnea, repeated post-obstructive pneumonia or bronchiectasis. The most common complications of EBTB are airway stenosis, atelectasis, hemoptysis and shortness of breath accompanied by wheezing despite the administration of ATD. Bronchoscopic intervention can support the acceleration of EBTB treatment, prevent repeated hospitalizations and improve the quality of life of patients. Acceleration of diagnosis and administration of ATDs in a complete and routine way is expected to reduce morbidity and even mortality rates in EBTB cases.

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INTRODUCTION

Pulmonary tuberculosis (PTB) continues to be a global health issue and is the main cause of mortality of infectious diseases. In 2021, the World Health Organization (WHO) reported 10.6 million cases of PTB, which amounts to about 134/100.000 individuals.[1] The incidence of PTB has shown 3.6% increase, leading to a mortality rate of within the period of 2020-2021. Indonesia is the second-highest contributor of PTB cases in 2021, after India, which is the greatest contributor globally.[2]

Endobronchial tuberculosis (EBTB) is defined as *Mycobacterium tuberculosis* (Mtb) infection of the tracheobronchial tract that is microbiologically or histopathologically confirmed tuberculosis with or without parenchymal involvement. This case is a form of PTB infection that is tricky to diagnose because of the infectious lesions can often be underdetected on sputum examination and chest X-ray. Active PTB patients represent 10-40% of EBTB cases, and bronchial stenosis occurs > 90% of cases. The incidence of EBTB is underdetected and unknown due to a bronchoscopy and thoracic computed tomography scan (CT scan) being rarely used for routine examinations in cases of PTB.[3]

EBTB is defined as an infection of the tracheobronchial tract with *Mycobacterium tuberculosis* that has been microbiologically or histopathologically confirmed, with or without lung parenchymal disease. Richard Morton, a doctor in England, was the first to report the involvement of the trachea and bronchi in PTB infection in 1698. Delays in treatment are often the result of issues in identifying EBTB. Bronchoscopy and thoracic CT scan can be recommended for follow-up examinations to confirm the diagnosis and examine bronchial lesions, including obstruction or stenosis.[4]

The main goals of EBTB treatment are the prevention of bronchial stenosis and the elimination of tubercle bacilli. EBTB cases show improved responses to the use of antituberculosis drugs (ATD). In some cases, the histopathologic appearance of endobronchial lesions does not always display the classic granuloma appearance of tuberculosis, despite the negative results of acid-fast bacilli (AFB) sputum. The diagnosis of EBTB can be difficult to determine related to the absence of classic PTB systemic symptoms, such as anorexia, weight loss, and nocturnal sweats.[5]

PATHOGENESIS

The exact pathogenesis of EBTB is still not completely known. Generally, there are five mechanisms of Mtb infection in EBTB: Direct spread of infection to the lung parenchyma, direct spread of Mtb from infected sputum, hematogenous spread, lymph node (LN) erosion into the bronchi, and flow of LN from the parenchyma to the peribronchial area.[6] EBTB infection can impact any layers of the tracheobronchial wall, including the muscularis lamina and cartilage. Ulcers, granulomas, fibroplasia, mucosal and submucosal infiltration, and tracheobronchial stenosis are among the various pathological changes (Figure 1).[7]

There are two phases in the pathophysiology of EBTB: the early and advanced stages. Hyperemia occurs in the mucosa during the early stage, and it shows in the submucosa when the next stage as the result of the infiltration of inflammatory cells, particularly lymphocytes.[8] EBTB can affect all branches of the bronchi during its course,

with the primary locations with the main bronchi, bilateral superior lobes, and middle lobe. The left bronchus is the location most likely to be infected with EBTB because infection in the LN spreads more quickly in the left bronchus than the right bronchus. This is because the LN is structurally located in the mediastinum and aortic arch nearer to the left bronchus.[9]

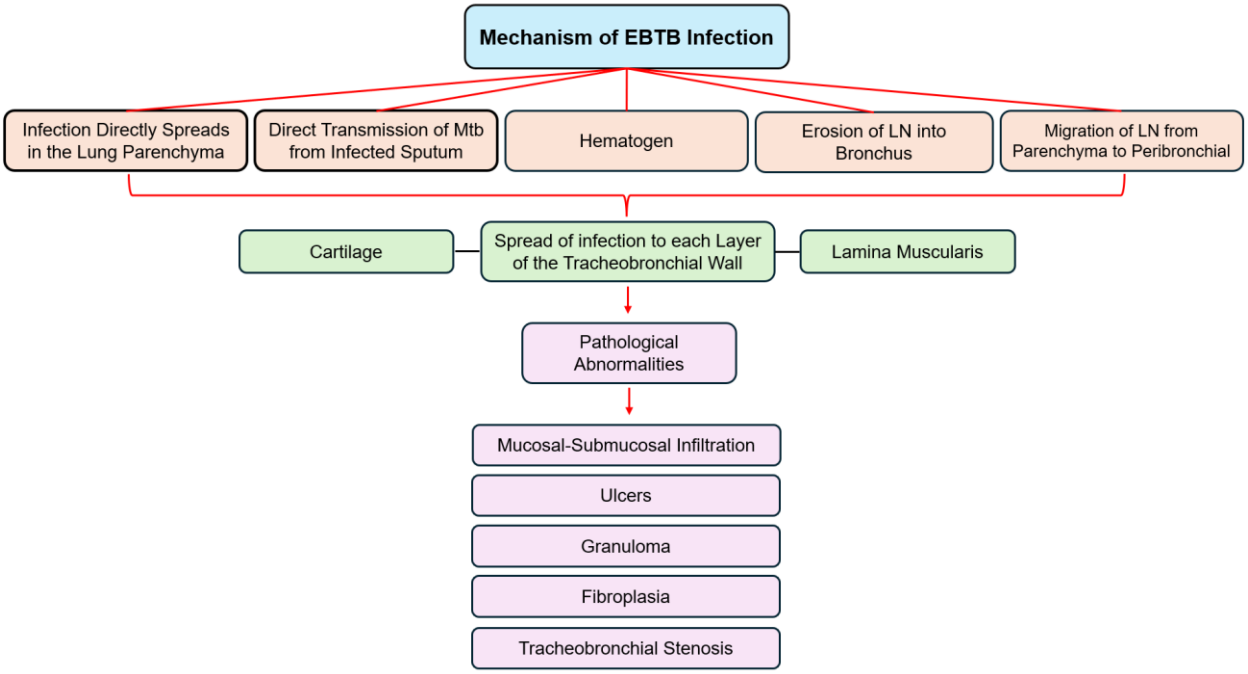

Figure 1. Pathological Abnormalities of EBTB[6,7]

The formation of an EBTB nodule is followed by the development of a caseous necrosis within the nodule and, finally, mucosal ulceration. The ulcer can either progress to the tracheobronchial wall and develop into an internal ulcer or become an inflammatory hyperplastic polyp that extends into the tracheobronchial lumen, like a tumor.[8] The incidence of tracheobronchial stenosis will reach 68% within 4-6 months and will continue to rise as the disease progresses, leading to the development of fibrous hyperplasia and contracture in the advanced stages. In addition to local factors, the development of EBTB is a complex phenomenon that is significantly affected from a variety of cytokines.[9]

The pathogenesis and progression of EBTB are also influenced by elevated levels of transforming growth factor-β (TGF-β) and interferon gamma in fluid of bronchoalveolar lavage (BAL). The development of bronchial stenosis through the course of the disease is associated with the alterations in TGF-β levels observed in serum after treatment.[9] The classification of EBTB by Jung et al. depends on the variety of levels involved. Single-level EBTB is characterized by the involvement of a single major tracheal or bronchial location. Multiple EBTB is defined as EBTB that affects two or more bronchi, and central EBTB has the potential to extend from the proximal to the bronchial lobe, potentially causing stenosis signs (Figure 2).[10]

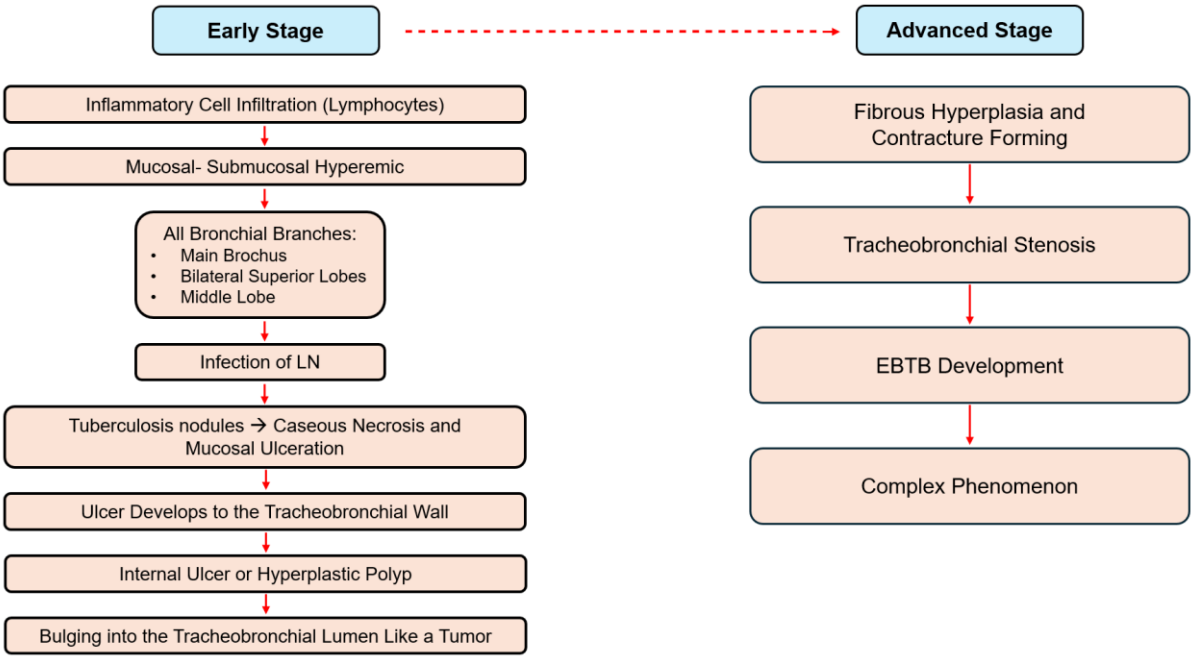

Figure 2. Mechanism of EBTB Occurrence[9,10]

DIAGNOSIS

Anorexia, fatigue, and weight loss belong to the symptoms of EBTB, which are as various as the systemic symptoms of PTB. It is reported that these symptoms manifest in more than 50% of patients.[11] Cough is the most common symptom in 70-80% of patients. When EBTB develops in cavitary PTB, dry cough or bronchorrhea is a common symptom. EBTB is indicated by a persistent cough that is responsive to concurrent steroid treatment with ATD but is not responsive to antitussives. While fever is present, coughing is typically moderate and may be associated with hemoptysis.[12]

Painful or dull chest pain at the sternum or parasternal is a symptom of ruptured LN. In certain lung areas, physical examination reveals decreased breathing noises, as well as ronchi and wheezing. Respiratory failure and lung collapse may result from symptoms of EBTB that involve the trachea. Liu et al. reported that pleural effusion may be a clinical symptom in EBTB cases as an outcome of delayed treatment. Central airway obstruction and failure of endotracheal intubation are life-threatening consequences of EBTB that can result in mortality.[13]

The diagnosis of EBTB is more complex compared to that of PTB. This is due to the fact that the indicators and symptoms of EBTB are not typical. A complete clinical examination of EBTB is extremely useful for the early identification and offering of appropriate treatment. Sputum examination and AFB culture are essential diagnostic procedures for patients suspected with EBTB. Bronchoscopy and thoracic CT scan are used as the main indicators are used as the main indicators to diagnose and assess bronchial involvement and surgical intervention.[14] In patients with EBTB, lung function evaluations are mainly restrictive. It's the result of chronic inflammation and modifications in parenchymal injury that extend above the stenosis.[15]

Sputum Examination

The AFB sputum examination is the most significant and frequently used method for the diagnosis of EBTB, despite the low diagnostic result. AFB sputum positivity

rates in EBTB are variable and with some studies showing that these numbers range from 16-53% of cases. In addition, early detection of EBTB should also be considered by clinical and physical examination even if AFB sputum examination is negative. Ulceration and mucosal involvement in EBTB patients are associated with a higher positive sputum result. In comparison to AFB sputum examination, AFB culture examination has a higher positivity rate. Therefore, it may be considered.[8]

Radiology

The diagnosis of EBTB can be difficult to establish because of a fact that chest X-rays usually produce normal results in about 10-20% of patients. For 10-40% of patients with active PTB, bronchial stenosis is identified. Infiltrates that are unevenly distributed in the affected lobe are common abnormalities on chest X-ray. Bronchostenosis, calcifications, cavities, bronchiectasis, intrathoracic lymphadenitis, and pleural effusion are some of the other chest X-ray findings that are based according to the severity.[16] Lee et al. showed that consolidation and atelectasis occurred in approximately 83.4% of chest X-ray for EBTB. The results for chest X-ray are one of the limiting factors in the diagnosis of EBTB, as it can be difficult to differentiate from asthma and lung cancer (LC) among older people.[17]

A thoracic CT-scan gives more detailed information than chest X-rays, including mediastinal lymphadenopathy, pleural effusion, nodules, and stenosis. Other results include endobronchial obstruction, fibrosis, and segmental bronchial narrowing with wall thickening.[17,18] Multiple lobar lesions, exudative shadows, and atelectasis are the most prevalent radiologic features, as noted by Qingliang et al. The goal of the examination is to present visualization before bronchoscopy. Patients with thoracic CT scan examination results that indicate EBTB images need to have bronchoscopy or a microbiology examination (Figure 3).[19]

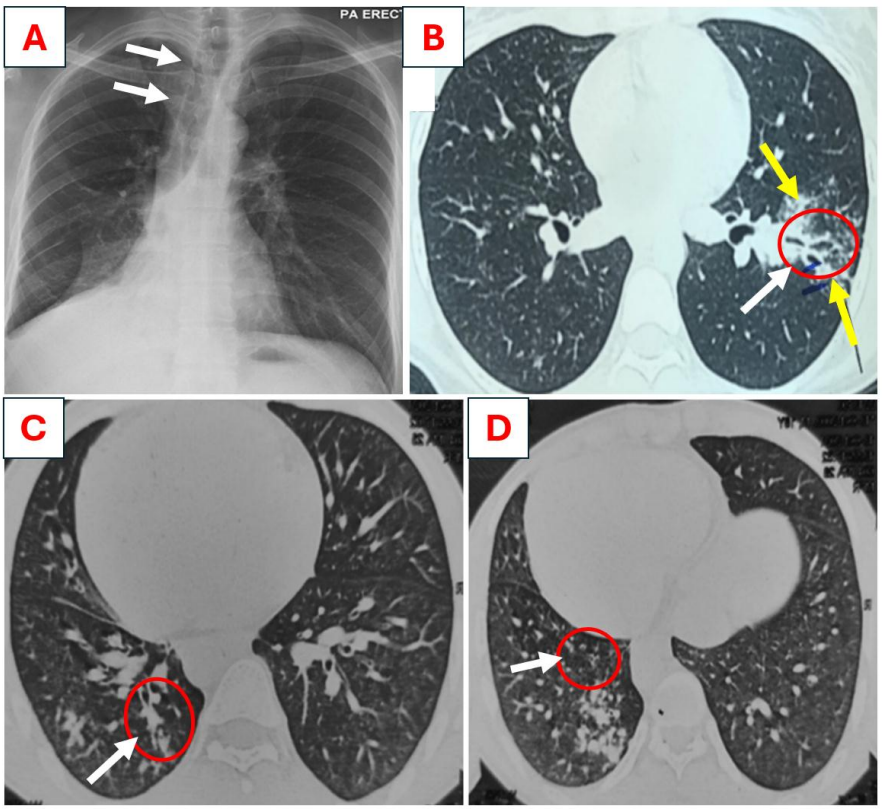

Figure 3. Radiologic Findings of EBTB. (A) Atelectasis of the Right Lung on Chest X-Ray; (B) Left Lung Nodules and Bronchiectasis on Thoracic CT Scan ; (C) Features of Tree in Buds on right Lower Lobe with High-Resolution Computed Tomography (HRCT); (D) Right Lower Lobe Nodules on HRCT

Bronchoscopy

Bronchoscopy is the most important technique for identifying the initial diagnosis and assessing the prognosis of EBTB. Several bronchoscopic procedures, including biopsy, bronchial brushing, bronchial washing, needle aspiration, bronchoalveolar lavage and endobronchial ultrasound (EBUS), are indicated as the most effective methods for identifying EBTB. Also, bronchoscopy is employed to exclude other concurrent or underlying diseases, such as malignancy. Studies conducted in China have indicated that bronchial brushing has a sensitivity of 84.88%, while bronchial washing has a positivity rate that ranges from 10-37.5%.[20]

Bronchoscopic specimen collection is important for the successful diagnosis of EBTB, as indicated by the presence of sputum examination and AFB culture positivity rate > 90%, while needle aspiration can be employed to obtain specimens from lobe segments that are inaccessible to biopsy instruments. EBTB is visualized through bronchoscopy to facilitate the differential diagnosis of other conditions. In addition, EBTB is classified according to bronchoscopic visualization, which comprises seven subtypes (Table 1).[18,19]

Table 1. Classification of Bronchoscopic Visualization of EBTB[19]

Subtype	Description
Active Caseous	Tracheobronchial mucosal wall is edematous, hyperemic and coated with a cheese-like yellowish-white coating
Hyperemic Edema	Edematous and hyperemic tracheobronchial mucosa
Non-specific Bronchitis	Tracheobronchial mucosa appears mild to moderate edema and hyperemic mucosa
Granular	Tracheobronchial mucosa is highly inflamed with rice grain-like nodules
Ulcerative	Tracheobronchial mucosa ulcers appearance
Tumorous	Hyperplastic focal tissue forms, tumor-like intraluminal masses
Fibrostenosis	Tracheobronchial lumen constricted by hyperplasia and fibrosis

The prospective study by Chung and Lee investigated the progression of EBTB by serial bronchoscopy, from the period of diagnosis to the conclusion of ATD treatment. The initial non-specific form of bronchitis is followed by the formation of submucosal tubercles. Next, the hyperemic granular and edematous type develops. The subsequent stage is identified by caseous necrosis, which results in the formation of tuberculous granulomas on the mucosal surface. Then, ulcers are formed and coated by caseous material as the inflammation extends through the mucosa.[8,19]

Hyperplastic inflammatory polyps develop from bronchial mucosal ulcers, and endobronchial tuberculous lesions resolve through fibrostenosis.[21-23] The erosion of tuberculous LN into the bronchus can occur in tumor-type EBTB.[24-26] The best prognosis is associated with the active caseous type and hyperemic edema type, which will result in fibrostenosis in patients. Granular, ulcerative, and non-specific forms of EBTB have an almost better prognosis (Figure 4).[19,27-29]

This form of tumor features a complex clinical course with a variety of progressions. The development of bronchial stenosis can be caused by such unpredictable modifications, despite the availability of adequate treatment.

The degree of progressing disease correlates strongly with the classification features of EBTB, with a distinctive appearance.[30-32] The management of EBTB through bronchoscopy encompasses balloon dilatation, stenting, laser, cryotherapy, and airway reconstruction.[33-35] Expertise in usage of both rigid and flexible bronchoscopy is necessary for the management of endobronchial lesions.[8]

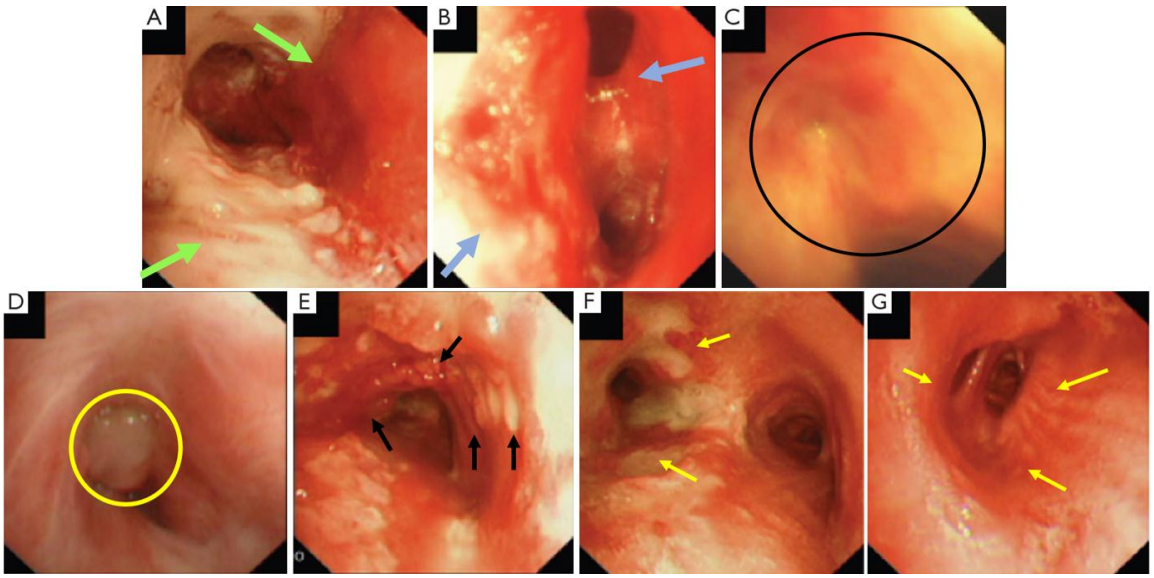

Figure 4. Bronchoscopic Visualization of EBTB. (A) Active Caseous; (B) Hyperemic Edema; (C) Fibrostenosis; (D) Tumorous; (E) Granular; (F) Ulcerative; (G) Non-specific Bronchitis.[19]

STRENGTH AND LIMITATION

This study can provide information related to the acceleration of diagnosis and the provision of complete and routine OAT which is expected to reduce morbidity and even mortality in EBTB cases. The limitation of this study is that it only focuses on Endobronchial tuberculosis.

CONCLUSION

PTB is a prevalent disease globally. The non-specific clinical symptoms of this form of EBTB demand special attention, as they have the potential to develop into severe complications of bronchial stenosis and delay the diagnosis of EBTB. Tracheobronchial stenosis can be prevented by early diagnosis and aggressive treatment with ATD treatment in the management of EBTB. Radiology, microbiology, and histopathology examinations are recommended along with bronchoscopy as the main diagnostic tool. Furthermore, the classification and prognosis of EBTB can be explained by the results of bronchoscopic visualization. Further research is needed to identify the disease's pathogenesis and progression in more detail.

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CONFLICT OF INTEREST

The authors confirm that they have no conflict of interst.

AUTHOR CONTRIBUTION

Writer, literature searcher, collecting data from literature: MOG and SII. Review and supervisio: ETMS.

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Role of Clinical Features and GeneXpert MTB/RIF Assay in Diagnosing Tuberculosis Among Toddler Patients in Surabaya

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GeneXpert MTB/RIF

Abstract

Tuberculosis (TB) is a leading cause of global morbidity and mortality, mainly in the age of 0-5 years old (toddlers). Several risk factors make toddlers more prone to TB infection. Although it commonly depends on clinical evidence, diagnosis of toddler TB can be done using microbiological confirmation like GeneXpert MTB/RIF Assay. However, this is still challenging to perform due to the low bacterial loads and difficulties in obtaining specimens. While prior studies focused more on the clinical aspects, this study will determine both the clinical and microbiological profiles of toddler TB patients at Dr. Soetomo General Academic Hospital Surabaya. This study was conducted using a retrospective approach. Samples were obtained using a total sampling technique from electronic medical records from January 2018 to September 2023. Variables collected include age, gender, type of TB, BCG vaccination status, history of household contact, nutritional status, symptoms, and GeneXpert MTB/RIF examination specimens and results. Among 125 toddler TB patients, the majority being female (57%), between the ages of 1–2 (45%), had BCG vaccination (86%), and without a history of household contact (63%). Most of the samples were malnourished (56%) and had cough as the symptom (62%). In GeneXpert MTB/RIF examination, gastric aspirate was the most collected specimen (52%) and the most common result found was negative (70%). In addition, two toddler patients were found to have DR-TB. In conclusion, while GeneXpert MTB/RIF assay predominantly resulted in negative, clinical features become the essential evidence to establish a diagnosis of tuberculosis among toddler patients.

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INTRODUCTION

Tuberculosis (TB) is a chronic, infectious disease caused by the species *Mycobacterium tuberculosis* (MTB).[1] Children aged 0-5 years old, also known as toddlers, have a higher risk of experiencing severe disease and mortality due to TB.[1] In 2022, it is estimated that 1-1.2 out of 7.5 million children in the world had progressivity from latent to active TB, more than half of it happened in toddlers.[2] Previous studies stated that in the range of 0-18 years old, TB is commonly found in the age of 0-4 years old due to the immunity system that has not been fully developed.[3,4]

Globally, only 42% of children under five with TB were diagnosed, compared with 70% of adults.[5] Diagnosis of TB can be established clinically or bacteriologically. As for the clinical signs and symptoms, a previous study showed that the majority of TB patients aged toddlers were dominated by males, had a history of household contact, and showed some symptoms such as chronic cough, fever, and lymphadenopathy.[6] Another study explained that the majority of toddler patients who were infected with TB had malnutrition and had not been vaccinated with BCG.[7] In general, toddlers tend to develop nonspecific symptoms similar to other diseases in the age group.[2]

The World Health Organization (WHO) recommends the utilization of rapid molecular tests using GeneXpert MTB/RIF as a screening and diagnostic tool for TB.[2] The result can be shown in two hours, which is shorter in duration than specimen culture, with 100% sensitivity and 95% specificity.[8] In a previous study, it was found that the most collected specimens in the GeneXpert MTB/RIF examination are gastric aspirate, sputum, cerebrospinal fluid, and tissue biopsy, respectively.[9] However, in toddlers, GeneXpert MTB/RIF results often show negative due to the paucibacillary characteristics of the microorganism. In specimen collection, toddlers also had difficulties in producing sputum, making toddler TB more difficult to diagnose and often ignored.[10]

There have not been many studies in Indonesia that discuss the GeneXpert MTB/RIF specimens and results specific to this highest-risk population. However, its sensitivity is lower than that of culture and clinical evidence (48%), making its application in children limited.[11] Based on the explanation above, this study aimed to determine the role of clinical features and GeneXpert MTB/RIF assay in diagnosing TB among toddler patients.

MATERIALS AND METHODS

This was a descriptive study using a retrospective approach. Data were collected from electronic medical records of toddler TB patients at Dr. Soetomo General Academic Hospital Surabaya. Samples in this study were toddlers (age 0-5 years old) who had been diagnosed positive for TB, either clinically or bacteriologically, and given TB treatment. Variables collected consist of age, gender, types of TB, nutritional status, history of household contact, BCG vaccination, symptoms, drug regimen, and the specimen and result of GeneXpert MTB/RIF examination. The inclusion criteria for this study were toddler TB patients in the range of January 2018 to September 2023. The exclusion criterion was patients with incomplete medical records according to the variables of this study. Technique used in this study was total sampling for the medical records of the patient that meet the inclusion criteria. Data were then processed using Microsoft Excel 2019 and presented in frequency distribution tables.

RESULTS AND DISCUSSION

This research was conducted from October 2023 to April 2024 at Dr. Soetomo General Academic Hospital Surabaya, East Java. A total of 125 medical records of toddler TB patients were obtained using total sampling technique according to inclusion and exclusion criteria, as shown in Figure 1. Based on domicile, 64 patients (51%) were from Surabaya and 61 patients (49%) were from outside Surabaya. This represents the role of Dr. Soetomo General Academic Hospital as a tertiary or referral hospital for TB patients.

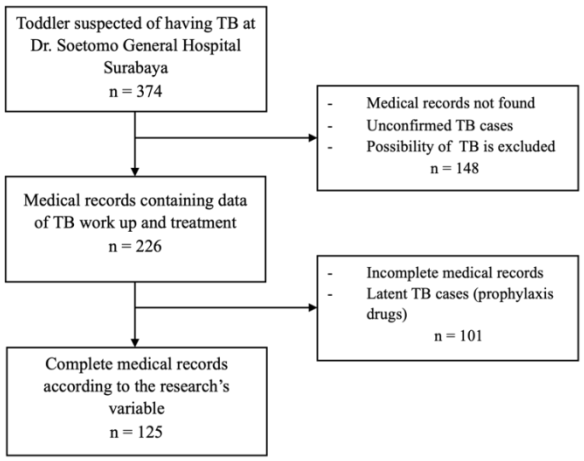

Figure 1. Inclusion and exclusion diagram

Figure 2 shows the annual sample amount, which indicates a fluctuation, yet relatively the same from 2018 to 2021. In 2022, there was a drastic surge compared to the year before, reaching the number of 35 samples. The amount kept rising in the period of January–September 2023 with a total of 47 patients. This event might be affected by several factors, such as data transfer from manual to electronic medical records and the COVID-19 pandemic which may affect people's health seeking behavior.

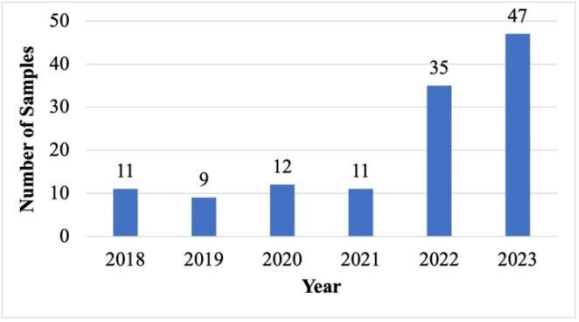

Figure 2. Annual distribution of research samples

Table 1. Clinical characteristics of toddler TB patients

Characteristics	N (%)
Age (n=125)	
<1 years old	31 (25)
1-2 years old	57 (45)
3-5 years old	37 (30)
Gender (n=125)	
Male	54 (43)
Female	71 (57)
Type of TB (n=125)	
Pulmonary	108 (86)
Pulmonary Only	77 (71)
Pulmonary and Extrapulmonary	31 (29)
Extrapulmonary	17 (14)
Bone and Joint TB	8 (47)
Meningitis TB	5 (29)
Lymphadenopathy TB	2 (12)
Abdominal TB	1 (6)
Skin TB	1 (6)
Nutritional Status (n=125)	
Severely Wasted	39 (31)
Wasted	27 (22)
Normal	52 (42)
Possible Risk of Overweight	3 (2)
Overweight	4 (3)
Obese	0 (0)
BCG Vaccination History (n=125	
Yes	108 (86)
No	17 (14)
Contact History (n=125)	
Yes	46 (37)
No	79 (63)
Symptoms	
Cough (n=125)	79 (62)
Weight loss / difficult to gain weight (n=125	50 (39)
Fever (n=125)	64 (50)
Night Sweats (n=125)	4 (3)
Short of Breath (n=125)	32 (25)

Samples were children between the ages of 0 and 60 months old, which then divided into three age groups: <1 year old, 1-2 years old, and 3-5 years old. In this study, most of the subjects were between the ages of 1 and 2 (45%). A study among children aged 0-14 years old in Indonesia revealed the highest amount of TB occurs in the age 1-5 years old.[10] Similar to that, another study found that pediatric TB patients were dominated by patients aged 1-5 years old (52%).[6] Children has a higher mortality and progressivity risk from latent infection to active disease, particularly for those aged under 2, having immunocompromise disease, or with malnutrition.[2,5] The high incidence of toddler TB could be the effect of immature immune system, which affect body's susceptibility to infection.[6] The immune cells in toddlers are inadequately functioning and predominated with Th2, compared to those in older children which are predominated by lymphocytes and Th1. Furthermore, there is a lesser amount of specific CD4+ T cells for MTB ESAT-6 (Early Secretion Antigen Target-6) in toddlers, mainly 0-3 years old, compared to older children (age 3-15 years old).[12]

According to gender, this study found that most toddler patients at Dr. Soetomo General Academic Hospital were female (57%). Prior study in the same hospital showed similar results, with a greater number of females in patients aged 0-4 years old.[3] Meanwhile, a study in Kediri, East Java discovered a higher number in male pediatric TB patients (56%).[6] This phenomenon might be influenced by several factors such as contact history, hormones, and body physiology. At toddler age, estrogens hormone, which acts as a protective factor to improve body immunity, cytokine, and macrophages, has not fully developed. Female tend to have weaker Th1 cells and fewer T CD8 and NK cells, which then makes the inflammation response become more massive.[13] However, a study stated that the greater probability of males developing TB than females were non-significant. Gender can be regarded as a risk factor after a child reach the age of puberty, by the role of sexual hormones in immunological dimorphism. In older age, males are then become more susceptible to TB due to increase exposure to outside world.[14]

Based on the Ministry of Health Republic of Indonesia, patients with pulmonary and extrapulmonary manifestation is classified as pulmonary TB.[15] This study found a higher frequency of pulmonary TB (86%), which linear to the result from prior study in the same hospital within the period of 2013-2017.[3] This primarily occurred due to the role of lungs as the *port d'entrée* of TB. *Mycobacterium tuberculosis* has a high affinity to oxygen and easily transmitted through droplet to enter the alveoli.[16] Bone and joint TB were the most found cases among extrapulmonary TB. This result is similar with a study in Beijing, whereas a study in Italy found peripheral lymphadenopathy TB dominated extrapulmonary cases (34.09%).[17,18] Bone and joint TB in toddlers originate from a primary infection site, typically the lungs or lymph nodes, which disseminates through the bloodstream.[19]

In this study, nutritional status was measured by the parameter of weight and height according to the anthropometric index of the WHO Child Growth Standard.[20] Apparently, from Table 1, most of the samples had normal nutritional status (42%). However, referring to the classification of malnutrition from the WHO, it was found that 56% of the samples had malnutrition. The WHO defined malnutrition as a condition with deficiency, overload, or imbalance of

energy intake and/or nutrition. This includes weight-to-height measurement which resulted in <-2 SD (wasting) or >+2 SD (overweight) based on WHO Child Growth Standard Median.[21] The outcome was different with another study in Sidoarjo, East Java, which found more toddler TB patients with normal nutritional status (32%) than poor nutritional status (27.2%).[16] Adequate nutrition might reinforce the immune system of the body, however this does not absolutely prevent toddler from getting infected with TB.[6] Tuberculosis and malnutrition correlated reciprocally. Malnutrition can increase severity and prolong recovery time from TB. This occurs due to an alteration in immune function, mainly in the interaction between macrophages and T-lymphocytes.[22] In addition, malnutrition can alter drug absorption and its further mechanism, which may cause treatment failure and downstream effects on treatment toxicity.[23] On the other hand, TB cause an increase in basal metabolic rate (BMR) to preserve body function, which then lead to weight loss. At the same time, TB patients often experience a decrease in appetite and gastrointestinal disorder, resulting in malnutrition.[22,24]

As much as 86% of the patients have received BCG vaccination. This result is similar with previous study in Jakarta which showed 80.6% of pediatric TB patients have been vaccinated.[25] In contrast, another study discovered only a small number of pediatric patients (30.8%) with history of BCG vaccination.[26] BCG vaccination has a variety of effectivity, ranging from 0-80%, this explains the probability of getting infected with TB despite having vaccinated before.[27,28] BCG vaccination could prevent the occurrence of severe TB, such as meningitis and miliary TB, and reduce the infection rate of MTB.[29] In young children, BCG vaccination can promote effective containment of the bacteria and protection against TB by increasing Th1 response towards MTB.[30]

Contact history remain an important factor in cases finding. Toddlers can only get infected by TB from a close contact history with either active or latent TB patient, hence it is required to perform history tracing from family and people nearby. In this study, the majority of the samples did not have any contact history (63%). This finding is similar to a study in Jakarta which discovered contact history in only 15.4% of pediatric patients.[26] Conversely, another study found contact history in most of pediatric TB patients (66%).[31] A study in a public health center in Surabaya mentioned that history of contact developed a higher likelihood of TB infection ($p<0.001$).[32] Incidence of toddler TB occurs not only by a single factor of contact history, but it is also influenced by other internal and external risk factors.[10]

Clinical symptoms that appeared the most among patients was cough (62%), followed by fever (50%) and weight loss/difficulty in gain weight (39%). The result was similar to a preceding study by Firnadi on children and adolescent TB patient at Dr. Soetomo General Academic Hospital.[3] Toddlers tend to develop unspecific symptoms that commonly mistaken as other diseases. However, clinical symptoms still become an important factor to establish a diagnosis of TB by using scoring method.[33] The least common symptom found was night sweats, it is linear to another study by Silva which discovered night sweats in only 10.9% of child TB patients.[34]

GeneXpert MTB/RIF Assay is a WHO recommendation for the screening and diagnostic testing of TB.[35] Culture confirmation remains a gold standard for diagnosing TB; however, it requires a longer

Table 2. Specimens and results of GeneXpert MTB/RIF assay

Specimens	Age (years)	GeneXpert MTB/RIF Results			N (%)
		MTB Detected		MTB Not Detected	
		RIF Sensitive	RIF Resistant		
Gastric Aspirate	0	6	0	15	21 (32)
	1-2	4	0	26	30 (46)
	3-5	6	1	7	14 (22)
	Total	**17 (25)**		**48 (75)**	**65 (52)**
Sputum	0	3	0	3	6 (20)
	1-2	4	0	10	14 (47)
	3-5	2	0	8	10 (33)
	Total	**9 (30)**		**21 (70)**	**30 (24)**
Tissue Biopsy	0	0	0	2	2 (13)
	1-2	1	0	3	4 (27)
	3-5	4	1	4	9 (60)
	Total	**6 (40)**		**9 (60)**	**15 (12)**
Cerebrospinal Fluid	0	0	0	1	1 (9)
	1-2	4	0	4	8 (73)
	3-5	1	0	1	2 (18)
	Total	**5 (45)**		**6 (55)**	**11 (9)**
Feces	0	1	0	0	1 (33)
	1-2	0	0	1	1 (33)
	3-5	0	0	1	1 (33)
	Total	**1 (33)**		**2 (67)**	**3 (2)**
Pericardium Fluid	0	0	0	0	0 (0)
	1-2	0	0	0	0 (0)
	3-5	0	0	1	1 (100)
	Total	**0 (0)**		**1 (100)**	**1 (100)**
Total		**38 (30)**		**87 (70)**	**125**

time to grow.[36] In this study, gastric aspirate was the most commonly used specimens (86%), which is in line with a 2018 study in Cipto Mangunkusumo Hospital, Jakarta.[37] GeneXpert MTB/RIF has a high sensitivity and specificity to detect MTB in gastric aspirate specimens of toddler patients.[38] Toddlers are usually facing difficulties in producing sputum, thus gastric aspirate is more frequently used than other specimens.[39]

From the examination, 70% of the specimens resulted in "MTB Not Detected" or MTB negative (Table 2). This was likely due to paucibacillary characteristics of MTB in toddlers. Moreover, toddlers commonly show difficulty in sputum expectoration and tend to swallow sputum during cough.[40] Results of GeneXpert MTB/RIF can be influenced several factors including specimen collection, processing, and storage.

Among 125 samples, two samples were found to have Drug-Resistant Tuberculosis (DR-TB) from the detection of resistance to rifampicin in the examination. From medical records, one patient was written to have Rifampicin-Resistance Tuberculosis (RR-TB) and the other had Multi Drug Resistance Tuberculosis (MDR-TB). Annual pediatric MDR-TB cases are estimated to reach the number of 30,000, yet only less than 5% are confirmed microbiologically.[41]

Rapid molecular test using GeneXpert MTB/RIF can also identify bacterial load using semiquantitative method. Measurement unit was indicated by cycle threshold (Ct) value, which is inversely related to bacterial load inside a specimen. This study found most specimens with very low level of bacteria, which means that the bacteria were found

during Ct >28 (Table 3). Low Ct value indicated a higher number of bacterial loads, and correlates with an increase in clinical severity of the patients.[42] Even with a low volume of specimen, rapid molecular test can still detect MTB DNA and bacterial amount inside specimen.[43] In order to obtain MTB isolates and avoid false-negative result, GeneXpert MTB/RIF is better to be performed together with MTB culture.[40]

Table 3. Bacterial load of the specimens (n=38)

Bacterial Load (based on Cycle threshold (Ct))	**Total N (%)**
Very Low (>28)	12 (31)
Low (22-28)	6 (15)
Medium (16-22)	3 (8)
High (<16)	0 (0)
No Data	17 (46)

The discussions above implied the importance of clinical evidence (signs and symptoms) in TB workup and diagnosis, despite commonly appearing nonspecific. In this study, since most of the patients had negative results in GeneXpert MTB/RIF Assay, most TB patients were diagnosed clinically rather than bacteriologically. As stated in a prior study, clinical signs and symptoms, patient history, and radiography are crucially essential for identifying TB in children, especially when the diagnostic test resulted in negative.[5]

STRENGTH AND LIMITATION

The strength of this study was comprehensive data of TB cases in specific high-risk population, especially the utilization of GeneXpert MTB/RIF as an early screening and diagnostic tool. The limitation of this study were some incomplete medical records which may potentially influence the accuracy of this study's findings. These findings may also differ in other settings or other healthcare system.

CONCLUSIONS

While GeneXpert MTB/RIF assay predominantly resulted in negative, clinical features become the essential evidence to establish a diagnosis of tuberculosis among toddler patients.

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ETHICAL CLEARANCE

The research protocol was approved by Ethics Commissions of the Faculty of Medicine, Universitas Airlangga, Surabaya, with grant number 1495/LOE/301.4.2/X/2023.

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CONFLICT OF INTEREST

All authors have no conflict of interest.

AUTHOR CONTRIBUTION

This study was designed by all authors. Reviewing the literature was done by SAP. Data collection was done by SAP and RAS. Data were analyzed by SAP, RJS, and RAS. Drafting manuscript was done by SAP and SPP. All authors have given approval for publication of this manuscript.

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Factors Analysis That Affecting The Treatment Success in Tb Patients in Situbondo Regency

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Abstract

Tuberculosis (TB) remains one of the top 10 lethal infectious diseases). In addition, the low case detection rate indicates that the community still has a large number of sources of transmission. Directly Observed Treatment Short-course (DOTS) strategy aims to reduce the new TB cases number by 80% and deaths by up to 90% in 2030. Drug-resistant TB cases especially multidrug resistant TB, exacerbate tuberculosis control because they receive TB treatment irregularly and do not comply to recommended treatment schedules, nonetheless, consistent treatment is critical to successful TB treatment. TB data in Situbondo district show that case detection was 911 out of 1539 cases or 59.14% and treatment success rate was 275 out of 911 cases or 30.2%. This study aims to examine the influence of knowledge, medication supervisors, family support, drug side effects, attitudes, length of treatment, and house physical environment on the treatment success through medication compliance factors. This research is explanatory with 196 respondents while the analysis uses SMART PLS 4.1.0.3. There is a direct influence of medication supervisors, family support, drug side effects, house physical environment and medication compliance and an indirect influence of medication supervisors, family support, drug side effects, and attitudes to TB treatment success. It is hoped that Public Health Centre officers can be more active to educate, detect TB suspect, and also supervise patient so compliance and treatment can be achieved. The patient's family can be more active in providing support during the treatment period for TB sufferers.

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INTRODUCTION

Tuberculosis (TB) is still a problem that is difficult to eliminate. Starting from low case detection, cases that have not been diagnosed and treated with the cure rate during 2020-2022 reaching 18-30%, as well as the complete treatment rate which has decreased.[1,2] Globally, TB cases during 2020-2022 continued to increase, namely 10 million cases to 10.3 million cases and increasing again to 10.6 million cases. Indonesia is in second place after India with a proportion of cases of 10% whose discovery and treatment coverage never reached the target of more than 85% during 2020-2022 with percentages of 41.7%, 47.1% and 74.7%.[2,3]

East Java is one of the provinces that accounts for nearly all tuberculosis cases in Indonesia. Out of 724,309 cases, there were 78,336 cases. Of these, 72.8% were discovered and treated. Furthermore, the treatment success rate fell short of the target of more than 90%, i.e., 88.4% in 2022. The case development rate indicates that, in Situbondo, there were 911 cases (59.14%) out of 1539 cases, of these, 275 cases were found and treated (30.2%).[4,5]

Cases of multidrug resistant (MDR) TB or TB resistant to antituberculosis medications challenge the management of TB. The number of MDR TB cases in Indonesia increased to 24,000, 27,000 and 31,000 in 2020-2022.[3] This was as a result of inconsistent therapy that doesn't occur within the allotted period. The goals of TB treatment are to cure patients, avoid medication resistance and prevent mortality. Thus, the effectiveness of TB treatment is influenced by patient compliance with medication.[6]

Many elements influence compliance, such as the patient's strong motivation, which keeps him from giving up and accepting his circumstances. Another consideration is the amount of time needed; patients may become bored and experience psychological strain when given extended periods of time. However, some patients are reluctant to stick with the treatment, because after one to two months, their symptoms start to get better. Furthermore, patients' non-compliance with therapy can also be contributed to drug side effects such as nausea, joint discomfort, redness and itching because they believe their reaction is growing worse.[6–8]

According to earlier studies, medication compliance and the adverse effects of anti-TB medications were directly correlated. People are less likely to take anti-TB medications when the adverse effects are severe.[9] High compliance with medications is correlated with improved self-efficacy, according to other study.[10] In addition, drug side effects and length of treatment have an impact on medication compliance among Indonesian TB patients.[11,12] Additionally, research indicates that 233 patients (40.04%) reported feeling better or no longer had symptoms, which accounted for the majority of the cause for patient noncompliance.[13] The aim of this study is to examine the variables influencing the success of TB patients' treatments in Situbondo Regency.

MATERIALS AND METHODS

This design of this study is explanatory. Patients with TB who have been declared cured or finished their treatment in 2023 represent the population. The study was carried out in the Situbondo district's health centers in April and May of 2024. Using the Slovin formula, the sample size was calculated, yielding 196 participants.

The study variable assesses the impact of medication compliance elements

on treatment outcome, including knowledge, medication supervisors, family support, drug side effects, attitude, length of treatment, and house physical environment. New TB patients with bacteriological confirmation who have been declared cured and finish treatment at the Situbondo health centre in 2023 meet the inclusion criteria. The exclusion criteria include less than six months of therapy, not being bacteriologically confirmed, and having an address registered outside of Situbondo. Questionnaire, hygrometer and/or mini particle counter, lux meter are all part of the apparatus. SmartPLS 4.1.0.3 was used for the test analysis.

RESULTS AND DISCUSSION

Results

Table 1. Distribution of respondent characteristics according to age, gender, last level of education, occupation and length of treatment among TB patients in Situbondo regency

Variable	Frequency (n)	Percentage (%)
Age		
10 – 19 years old	5	2.55
20 – 44 years old	79	40.31
45 – 60 years old	65	33.16
> 60 years old	47	23.98
Sex		
Male	103	52.55
Female	93	47.45
Education		
No school	36	18.37
Elementary school	62	31.63
Junior high school	28	14.29
Senior high school	61	31.12
College	9	4.59
Employment		
Unemployment	78	39.80
Farmer	42	21.43
Trader	19	9.69
Labor	24	12.24
Fisherman	3	1.53
Private employees	17	8.67
Civil servant/army/police	2	1.02
Other	11	5.61

Table 1 shows that out of the 196 respondents, the majority of respondents, 79 people (40.31%) were between 20-44 years old, 103 people (52.55%) were male, 62 people (31.63%) had completed elementary school and 78 people (39.80%) were unemployed.

Table 2. Knowledge level

Variable	Frequency (n)	Percentage (%)
Good	135	68.88
Sufficient	2	1.02
Less	59	30.10
Total	196	100

Table 2 shows that the majority of respondents, 135 people (68.88%) have a good deal of knowledge on TB.

Table 3. Medication supervisor

Variable	Frequency (n)	Percentage (%)
Active	142	72.45
Not Active	54	27.55
Total	196	100

Table 3 shows that the majority of respondents, 142 people (72.45%), have a medication supervisor who plays an active role in TB patients.

Table 4. Family support

Variable	Frequency (n)	Percentage (%)
Good	133	67.86
Moderate	13	6.63
Lack	50	25.51
Total	196	100

Table 4 shows that the majority of respondents, 133 people (67.86%) experienced good family support.

Table 5. Drug side effects

Variable	Frequency (n)	Percentage (%)
No	29	14.80
Yes	167	85.20
Total	196	100

Table 5 shows that the majority of respondents, 167 people (85.20%), experienced drug side effects.

Table 6. Attitudes

Variable	Frequency (n)	Percentage (%)
Good	147	75.00
Bad	49	25.00
Total	196	100

Table 6 shows that the majority of respondents, 147 people (75.00%) had a good attitude.

Table 7. Length of treatment

Variable	Frequency (n)	Percentage (%)
≥ 6 months	190	96.94
< 6 months	6	3.06
Total	196	100

Table 7 shows that majority of respondents, 190 people (96.94%) had undergone treatment for at least six months.

Table 8. House physical environment

Variable	Frequency (n)	Percentage (%)
House Density		
Adequate	142	72.45
Not Adequate	54	27.55
Ventilation Quality		
Adequate	138	70.41
Not Adequate	58	29.59
Living Room Lighting		
Adequate	141	71.94
Not Adequate	55	28.06
Bedroom Lighting		
Adequate	135	68.88
Not Adequate	61	31.12
Living Room Humidity		
Adequate	138	70.41
Not Adequate	58	29.59
Bedroom Humidity		
Adequate	139	70.92
Not Adequate	57	29.08
Living Room Temperature		
Adequate	129	65.82
Not Adequate	67	34.18
Bedroom Temperature		
Adequate	133	67.86
Not Adequate	63	32.14
Floor Condition		
Adequate	126	64.29
Not Adequate	70	35.71
Wall Condition		
Adequate	126	64.29
Not Adequate	70	35.71

Based on Table 8, it can be seen that majority have an adequate house density requirements, namely 142 people (72.45%), have an adequate ventilation quality requirements, namely 138 people (70.41%), have adequate lighting in the living room and bedroom requirements, namely 141 people (71.94%) and 135 (68.88%), have an adequate humidity in the living room and bedroom requirements, namely 138 people (70.41%) and 139 people (70.92%), have an adequate living room and bedroom temperature requirements, 129 (65.82%), and 133 (67.86%), have an adequate floor and wall condition requirements, specifically 126 (64.29%), both in living room and bedroom. Overall, various indices of the house physical environment of TB patients in Situbondo regency show that the majority have adequate needs.

Table 9. Medication compliance

Variable	Frequency (n)	Percentage (%)
Successful	149	76.02
Unsuccessful	47	23.98
Total	196	100

Table 9 shows that the majority of respondents, 149 people (76.02%) classified as successful medication.

Table 1. Hypothesis result

Variable	P values
Medication supervisor ≥ TB treatment success	0.001
Family support ≥ TB treatment success	0.007
Drug side effects ≥ TB treatment success	0.013
Length treatment ≥ TB treatment success	0.065
House physical environment ≥ TB treatment success	0.002
Medication compliance ≥ TB treatment success	0.000
Knowledge x medication compliance ≥ TB treatment success	0.469
Medication supervisor x medication compliance ≥ TB treatment success	0.045
Family support x medication compliance ≥ TB treatment success	0.010
Drug side effect x medication compliance ≥ TB treatment success	0.004
Attitude x medication compliance ≥ TB treatment success	0.010
Length treatment x medication compliance ≥ TB treatment success	0.305

According to Table 10, the statistically significant variables that have a direct influence on TB treatment success are medication supervisor, family support, drug side effects, house physical environment, and medication compliance. The variables that have an indirect influence on TB treatment success through medication compliance are medication supervisor, family support, drug side effects and attitude.

Discussion

The Influence of Medication Supervisor on TB Treatment Success

The medication supervisor is the first person who communicates with the patient about their treatment. To ensure recovery and prevent drug resistance, every new pulmonary TB patient receiving treatment must be closely monitored while consuming the medication. Before treatment begins for the first time, pulmonary TB patients and their medication supervisors must receive a brief education about TB including symptoms, drug side effects and treatment as well as the importance of daily medication swallowing monitoring to ensure patient compliance. The medication supervisor will remind of the medication-taking schedule, monitor the patient's swallowing, take the patient for regular check-ups and assist if there are any side effects.[14]

The results of the study showed that there was a statistically significant relationship between medication supervisors and the success of TB treatment (p-value = 0.001). The majority of TB sufferers have a medication supervisor who plays an active role in the treatment of TB sufferers. A total of 142 people or 72.45% of respondents answered that the supervisor's role was to swallow medicine properly. Usually the person supervising the swallowing of medicine is the closest family member or cadre.

The results of the research are in line with research conducted by Maulidya et al., 2017[15] which states that medication supervisor influences TB treatment success (p-value = 0.026). The majority of TB sufferers who have medication supervisor were declared cured, namely 18 people (90%) compared to those who did not have medication supervisor, namely two people (10%). The risk of recovery is 13.5 times higher for medication supervisors than those without it. Another study, similar to Mokambu et al. (2023)[16], found that of the 29 people who were successful in TB treatment, 20 people (68.97%) had a medication supervisor that played a good role, as opposed to a medication supervisor that played a fair and poor role, namely eight people (27.59%) and one person (3.45%), respectively. Of the 21

respondents who had a good medication supervisor, 20 people were successful in treatment, while one was unsuccessful.

The Influence of Family Support on TB Treatment Success

Family support consists of encouraging patients to take their medication, expressing sympathy and care, and not avoiding patients' illnesses. Family support is related to TB patient medication compliance, which should be a family member, such as a child or partner, due to their trustworthiness. They can monitor the patient till they actually swallow the drug every day, regularly and on time according to the dose prescribed by the health worker.[17] Support from the closest family which will boost self-confidence. Someone with high self-efficacy will appear optimistic, confident and have a positive outlook.[18]

The support includes reminding the patient of control schedule, taking medication on time and paying attention to patient complaints so that the patient feels comfortable, cared for and loved by the family, all of which contribute to good physical and mental health. Aside from that, the patient's family can also provide financial support, close supervision, and assistance in getting to the hospital so that the patient feels that there is a family who is always willing to accompany and help them financially. Other support involves providing information about the patient's TB, encouraging them not to give up and recovering fast from their condition and providing basic necessities.[19]

This research shows that there is a statistically significant relationship between family support and the success of TB treatment (p-value = 0.007). This happens because the majority or 67.86% of TB sufferers receive good family support compared to sufficient family support, namely 6.63% and less, namely 25.51%. The support provided can be in the form of searching for information, accompanying during consultations, reminding the control schedule to the Health Centre.

Research conducted by Happi et al. (2021)[20] shows that there is a relationship between family support and TB treatment success (p-value = 0.004). The majority of the help supplied was positive, specifically information (86.7%), emotional support (90%), instrumental (90%), and appreciation (96.7%). Information support on treatment is critical for better understanding patient condition including treatment outcomes and progression of TB patient. Emotional support from loved ones can boost patients' excitement by providing comfort and a sense of belonging. Instrumental support offers practical assistance with money, time, facilities, therapy, food and rest. Appreciation support can be provided by offering assistance, encouragement, praise, and including TB patients in decision-making to increase convenience and passion for TB patients.

The Influence of Drug Side Effects on TB Treatment Success

Side effects are an adverse reaction that plays a role in treatment decisions. The occurrence of adverse drug reactions has the potential to result in patients either failing to adhere to their prescribed medication regimen or even discontinuing their treatment.[21,22] The drugs that are often used in the treatment of TB are Isoniazid, Rifampicin, Pyrazinamide, Streptomycin and Ethambutol which will cause side effects, both mild or severe. The large number of side effects in the first and second weeks is due to the initial stage of the drug reacting with antibodies so that allergic reactions/side effects appear. The use of

causes various side effects and the most common ones are redness of the urine due to Rifampicin, delivery pain due to Pyrazinamide, nausea due to most antituberculosis drugs (ATDs) and tingling due to Isoniazid. Drug side effects often occur during the initial treatment period, namely in the first and second months, which is the intensive phase.[23] Drug side effects result in the patient not taking medication regularly or even stopping it.[21]

The research shows the influence of drug side effects on the TB treatment success is statistically significant (p-value = 0.013). In this study, it was found that 167 people (85.20%) feel drug side effects. The majority,157 people (80.10%), experienced mild and severe effects simultaneously. The complaints most frequently felt by respondents were stomach pain (mild side effects) and reddish itching (severe side effects) both at 80.10%. However, it does not cause the patient any distress and only occurs at the beginning of treatment, otherwise the patient feels better and has fewer complaints.

This is consistent with prior studies by Amining et al. (2021) [24] that found drug side effects are statistically significantly related to TB cure rates. The majority, 87 people (89.69%), of TB patients who experienced drug side effects were declared cured, whereas 10 people (10.31%) did not recover. The side effect of stomach ache is produced by pyrazinamide and can be lightened by drinking warm water or ginger; however, if the complaint persists, the patient should visit a doctor or health service provider. Also, Rahajeng et al. (2021) stated that all types of TB drugs can cause itching and redness.[25,26] If a person's itching occurs without a rash and there is no evident cause other than anti-TB drugs, the suggested approach is to try symptomatic treatment with antihistamines and skin moisturizers, with TB medication continuing while observed. If a skin rash appears, all anti-TB drugs must be temporarily stopped, and drug challenge implemented.[27]

The Influence of Length of Treatment on TB Treatment Success

Treatment is the way to control the large number of TB sufferers. To destroy tuberculosis bacteria, the treatment lasts 6 to 8 months. The first two months are spent intensively, followed by four months of continuing. The duration of TB treatment is the period of time that pulmonary TB sufferers undergo treatment aimed at preventing recurrence, resistance to ATDs, breaking the chain of transmission, and death.[14]

Long treatment times will cause boredom, allow for non-compliance and result in people dropping out of treatment during the healing period for various reasons, including feeling healthy, or economic factors. Apart from that, the longer TB treatment takes, the greater the stress level of TB sufferers. Many patients after entering the advanced phase stop treatment because they feel they have recovered. In fact, non-compliance with treatment will cause failure and recurrence, thus, sickness continues to spread and resistance develops. If the combination of drugs used is inadequate (type, dose and duration of treatment), pulmonary TB germs will develop into drug-resistant germs.[14] This can increase the risk of morbidity, mortality and drug resistance both in sufferers and in the wider community.[28,29]

The study found that the length of treatment has no direct effect on the outcome of TB treatment (p-value = 0.065). The majority of respondents, namely 190 people (96.94%), had undergone treatment for ≥ 6 months. They continued to carry out treatment even though it required feeling bored and

takes a long time, because the sufferer wants to recover. The minimum TB treatment period is six months with the aim of preventing resistance and killing inactive germs. Repeated sputum examinations are used to track the progress of TB treatment conducted at the final intensive stage (2nd month), one month before the end of treatment (5th month), and at the end of treatment. If all three findings are negative, it is said to be cured or completely treated.[30]

Another factor is that respondents do not want to repeat therapy; therefore, the time period is extended and the dose of medication increases. This is consistent with study conducted by Nasution et al (2023) [31] showing the sufferer's desire to recover fast, aided by motivation from medication supervisor, does not make sufferers feel frightened even though they experience drug side effects such as nausea and dizziness in the early stages of treatment. Motivation is a driving force in the form of the desire to achieve a goal. Motivation will encourage, stimulate, move, provide the background, carry out and control a person and direct healing actions. Motivation is also influenced by knowledge. The higher the amount of information, the greater the desire to recover. The majority of respondents in this study had strong knowledge, with 68.88%. Counseling, medication supervisor and family support can enhance motivation.

The Influence of House Physical Environment on TB Treatment Success

The house environment can affect the health of its residents. Occupancy is related to the floor area of the house which is adjusted to the number of residents. The denser the number of residents, the faster transmission occurs.[32] Density is said to meet the standards if it exceeds 8 m^2/person. Humidity also contributes to the spread of tuberculosis. TB and other harmful bacteria grow in high-humidity conditions (>70%). This happens because more than 80% of the volume of bacterial cells are formed from water. So they can grow and survive there.[33,34]

Air quality is influenced by indoor temperature and humidity as well as sunlight that can enter the room. Exposure to direct sunlight or hot air temperatures causes droplets of *Mycobacterium tuberculosis* bacteria to evaporate into the air, aided by the movement of wind currents which fly along the air flow. Lack of sunlight entering the house and poor ventilation greatly affects air circulation and creates a damp and dark atmosphere, causing germs to survive for days to months in the house. The spread will also be faster under these conditions.

The results of the research show that there is a relationship between the house physical environment and the TB treatment success with a p-value = 0.002. The quality of the house physical environment shows that all indicators meet health requirements. These results are in line with research by Sahadewa et al (2019) and Mardianti et al. (2020)[31,34] which states that there is a significant relationship between density (p-value = 0.002), ventilation (p-value = 0.006), light (p-value = 0.024), humidity (p-value = 0.034), temperature (p-value = 0.006), and air quality (p-value = 0.015) which were all associated with the incidence of pulmonary tuberculosis. Thus, the quality of the house physical environment, which mainly fits the standards, has a role on the TB treatment success.

The Influence of Medication Compliance on TB Treatment Success

Compliance is key to successful treatment. Medication must be taken regularly according to schedule. Especially in the intensive phase, most smear positive

TB sufferers can become negative (conversion) within 1-2 months. TB treatment, which is divided into intensive and advanced stages, aims to prevent resistance and kill dormant germs. The final results of the examination with a negative conversion as well as a statement of recovery and complete treatment stated by the doctor indicate the success of the treatment.[17,35]

Patients in this study said that they took medication regularly to get better quickly. They argue that they do not want to repeat treatment for a longer time (could be eight months). Apart from that, the majority of patients receive good family support, which increases their enthusiasm and motivation to complete their treatment completely. Even though there were side effects from the medication, they do not interfere with the respondent's daily activities. Patients also feel better after taking the medicine and believe that the medicine they are taking has the benefit of curing the patient.

This is in accordance with research by Meyrisca et al. (2022)[36] that there is a relationship between compliance and recovery rate (p value = 0.000). The more obedient a patient is in taking medication, the greater the chance of successful treatment. Other research also finds the same result. Of the 62 people who complied, 100% were successful in treatment.[37] There are numerous factors that contribute to medication compliance, including the presence of information and education from health workers to complete treatment until completion, support from the medication supervisor, which plays a role in providing encouragement and motivation so that sufferers do not give up on treatment, positive attitudes, and good family support and willingness. Patients that are motivated to recover are more likely to complete their treatment.

The Influence of Knowledge on TB Treatment Success through Medication Compliance

Medication compliance is affected by one's knowledge of tuberculous patients. The better a person's knowledge about TB and its treatment, the more aware and obedient they will be to undergo a regular treatment program. Knowledge can influence sufferers' understanding of TB disease, which is a dangerous and contagious disease. In addition, knowledge will shape a person's actions (open behavior). Benjamin Bloom stated that the domain of behavior is knowledge, attitudes and actions. Attitudes and actions without good knowledge will not last long. On the other hand, good knowledge will be meaningless if it is not balanced by attitudes and actions.[38]

The results of this study show that there is no significant influence between knowledge and treatment success through medication compliance with a p-value = 0.469. This happened because the majority of respondents' knowledge level was classified as good, namely 135 people or 68.80%. At the time of the interview, the sufferer was aware that tuberculosis was an infectious disease, yet his views and actions were inversely proportionate. For example, some patients believe that tuberculosis is a curse, a genetic sickness, or a mental illness. So, in addition to TB therapy, people are seeking for other therapeutic options that align with their beliefs.

Moreover, good knowledge is not necessarily followed by good attitudes and actions because the knowledge process consists of (six categories, namely knowledge in remembering the material/ information studied, understanding, applying information to real situations, analyzing, making hypothesis and evaluating its benefits. Knowledge is also

supported by educational background.[39] Further investigation reveals that the bulk of respondents (90 persons, 45.92%) have a low educational background (primary to junior high). The higher the level of education, the easier it is to obtain information. According to Darsini et al. (2019)[40], someone who has obtained formal education is accustomed to thinking logically, detecting problems, analyzing, and attempting to solve them. As a result, if higher education provides someone with useful knowledge, it is believed that their attitudes and actions will be positive as well.

This is in accordance with research by Sari et al. (2016)[41] that there is no significant relationship between knowledge and compliance in pulmonary TB sufferers (p-value = 0.619). Good knowledge does not guarantee that it will be directly proportional to the sufferer's behavior. The patient's knowledge which is not followed up with attitude is the cause of the lack of influence between knowledge on the patient's recovery. Knowledge about TB and confidence in treatment progress influence sufferers to choose to complete treatment. Cultural beliefs also influence healing. This means that whether the patient's knowledge is high or low does not affect their recovery.[15,42]

The Influence of Medication Supervisor on TB Treatment Success through Medication Compliance

A medication supervisor is someone who is trusted to monitor and ensure compliance and recovery for TB sufferers during treatment. Medication supervisors can supervise, provide support so that patients want to seek regular treatment and provide education or accompany TB sufferers in taking anti-TB drugs.[16] In this case, they ensure that the patient swallows all the medication regularly and according to standards. A medication supervisor is expected to be able to understand the procedures for taking medication as well as everything related to pulmonary TB disease.

The results of the study show that medication supervisor has an indirect effect on the TB treatment success through compliance to taking medication (p-value = 0.045). This is in line with research conducted by Aini and Astuti (2020)[31] which states that medication supervisors that play an active role have a greater impact on medication adherence than medication supervisors that play a less active role. Research by Ali et al. (2019)[29] also shows a relationship between medication supervisor and medication compliance (p-value = 0.001). Medication supervisors that play a less active role are 4.995 times more likely to cause TB sufferers to become non-compliant with treatment compared to medication supervisors that play an active role.

Family support and acceptance from family members will give sufferers the energy and confidence to make more effort to learn and accept subjective situations such as anxiety, sadness, guilt, annoyance and boredom.[43] Medication supervisors whose role is to directly see TB sufferers swallowing medication have a 20.25 times greater risk of medication compliance. Therefore, the medication supervisor plays an important role in monitoring patient compliance while taking medication until completion of treatment according to the TB treatment program strategy, namely the Directly Observed Treatment Short Course (DOTS).[44]

The Influence of Family Support on TB Treatment Success through Medication Compliance

Family support is very necessary in determining the continuity of treatment. TB

sufferers will feel motivated to take medication according to the instructions given. The support provided can be in the form of emotional support, namely communicating love, care and trust to family members. Other support is instrumental support, namely support in terms of goods or services, for example giving money and helping with housework. Information support is also needed because it can provide advice, suggestions, instructions and provide information, for example about the importance of the treatment being undertaken and the impact of not complying with treatment. Apart from that, the support provided can be provided by guiding and dealing with split problems and can be someone in the same situation or similar experience who makes the sufferer feel supported by various ideas and feelings.[14]

The research results of family support have a direct statistical effect on the success of TB treatment (p-value = 0.010). In this case, it was found that the majority of respondents, namely 133 people (67.86%), had received good family support. This is in line with research by Nasedum et al. (2021)[45] showing that there is a significant relationship between patient attitudes and medication compliance (p-value = 0.000). Furthermore, good family support tends to be more compliant, namely 29 people (64.4%), compared to those who are not compliant, namely eight people (17.8%). Another study by Fitriani et al. (2019)[46] also found that 10 people (32.3%) complied to taking medication because they had high family support. Families who live in the same house always remind the respondent about the schedule for taking medication and encourage the respondent to recover and take the sufferer to be examined. So it is better for the child or partner to become a medication supervisor because they are more trustworthy and provide emotional support.[46]

Family support that can be provided is reminding the patient of the patient's control schedule, taking medication on time and paying attention to the patient's complaints so that the patient feels comfortable, cared for and loved by the family, which can affect the patient's physical and mental health. This can reduce the effects of anxiety by directly improving the mental health of individuals or families because sufferers think their family can help overcome their problems. Family support can help patients feel less pain, recover more quickly from their illness, adjust better, and recover faster.[47]

The Influence of Drug Side Effects on TB Treatment Success through Medication Compliance

Most sufferers feel they cannot tolerate the side effects of anti-tuberculosis drugs (ATDs) experienced during treatment. The severity of the side effects experienced will have an impact on the patient's survival and can even result in discontinuation of treatment (loss to follow up) from treatment.[48] The loss to follow up rate should not be more than 10% because this will result in a high proportion of retreatment cases in the future due to ineffective TB control. Therefore, it is very important to maintain the patient's clinical condition during the treatment period so that serious side effects can be identified immediately and managed appropriately.[9] Patients also need to be informed about the side effects of ATDs so that patients do not misunderstand what they are experiencing which can result in drug withdrawal.

The result of research is TB sufferers said that even though they had side effects while undergoing treatment, they continued to take the medication.

Patients who are aware of the side effects of drugs will respond well to these complaints. Apart from that, sufferers also feel that their complaints do not interfere with their daily activities, some even feel that TB medication has made them better from being unable to move and just lying on the bed to being able to move more actively and increase their appetite.

The results of this study show that the drug side effect through medication compliance does not statistically influence the success of treatment (p-value = 0.004). So it can be said that the majority of respondents, namely 174 people (88.8%), had relatively mild drug side effects. The mild side effects of the drug allow patients to tend to be compliant during the treatment period as in line with the research from Aini and Astuti (2020)[49] that drug side effects and medication compliance in pulmonary TB sufferers are statistically related. Respondents in this study stated that the most frequent complaints were stomach pain, itching and redness, nausea, discoloration of urine and tingling. This means that most respondents tend to experience mild and severe side effects compared to severe side effects.

On the other hand, some drug side effects were serious and 41.7% of patients were compliant during treatment while 58.3% were not. Another reason for patients complying is because there is motivation from to quickly recover from their illness.

The Influence of Attitude on TB Treatment Success through Medication Compliance

Apart from knowledge, attitude is also a factor in patient compliance in taking medication. Attitude plays a role in a person's behavior and decision-making during the healing process. A positive attitude that a person has toward their illness will lead to positive health seeking behavior, thereby further encouraging a person in their efforts to complete treatment.[28]

Based on the research results, the patient's attitude has an indirect influence on treatment success through medication compliance (p-value = 0.010). Most of the respondents, namely 147 people (75%), had a moderate attitude with medication compliance which was also moderate, namely 149 people (76.02%). This is in accordance with the theory that plays a role in attitude change including willingness, identification and internalization, it is possible that the sample is in the willingness or identification stage.

The process of willingness occurs when an individual is willing to accept influence from other people or from other groups in the hopes of receiving a positive reaction or response (such as praise or support) from the other party. The identification process occurs when an individual imitates the behavior or attitude of a person or the attitude of another group because this attitude is in accordance with what he considers to be a pleasant form of relationship with the other party. Meanwhile, internalization occurs when an individual accepts influence and is willing to behave according to that influence because this attitude is in accordance with what he believes and is in accordance with the value system he is in compliance with.[28]

This is in line with research by Maulidya et al. (2017)[15] and Ardat (2020)[50] that there is a relationship between patient attitudes and the success of pulmonary TB treatment (p-value = 0.008). Patients who have a good attitude during treatment have a 4,333 times greater chance of recovery compared to patients with a fairly good attitude. The respondent's attitude of being willing to accept doing something that is

considered right will influence his behavior. The more the patient agrees to take medication regularly, the more the patient will increase their regularity in taking medication. On the other hand, a negative attitude or lack of agreement with a treatment encourages sufferers to behave non-compliantly, both in terms of repeat treatment and taking medication.[50]

The Influence of Length of Treatment on TB Treatment Success through Medication Compliance

Duration of treatment is the period of time required to carry out treatment with the aim of preventing recurrence, ATDs resistance, breaking the chain of conversion and death. The results of research by Dwiningrum et al. (2021)[51] show that there is a significant relationship between length of treatment and compliance to taking medication (p-value = 0.001). Respondents who underwent treatment for >2 months had a 2.7 times greater risk of non-compliance in taking medication compared to those who underwent treatment for <2 months. TB sufferers must take medication regularly for six months, which has a big impact on curing the disease. If not, it can result in drug resistance so that treatment costs a lot. Apart from that, it can have worse effects than not being treated at all, for example sufferers can relapse at any time. If treatment is carried out for a longer period of time it will have an impact on stress levels. TB sufferers can feel bored of taking medication for quite a long time and every day, coupled with the side effects of the medication which can interfere with daily activities, which has an impact on stress levels.

This is in line with research conducted by Panggayuh et al. (2019)[52] found that there is no relationship between the type of patient and the success of pulmonary TB treatment. Category 1 (for new cases) is given for six months with two months of intensive phase and four months of advanced phase. Category 2 (for old cases) is given in two stages with three months in the initial stage and five months in the advanced stage. Patients with old and new cases of pulmonary TB have the same chance of success in treatment as long as they take ATDs according to the guidelines and at the specified time. The research results show that the majority of TB sufferers have a medication supervisor that actively supports TB treatment (72.45%) and good family support (67.86%), so that sufferers will not feel bored and will still have the desire to complete treatment until they are declared cured. or have completed treatment by a health professional or doctor.

STRENGTH AND LIMITATION

The study examines respondents of all ages who had been declared cured or completed treatment; it is hoped that by knowing the factors that influence the success of treatment, TB control can be better. The method is explanatory research seeks to identify and ensure cause and effect relationships between variables and to know how phenomenon will change or vary within a relationship with other variables.

The limitation of this study was the institutional-based nature of the study which might not apply for other TB patients who didn't visit the institution. Self-report of compliance to medications could also be affected by recall bias. Thus, we suggest further study to investigate patients in hospital. Other variables that can also be examined are the role of health workers, costs, and nutritional status of patients. Qualitative research methods can also be used in the future.

CONCLUSIONS

The conclusion is that there is a significant direct influence between drug side effects, family support, medication supervisors and house physical environment on the success of treatment for TB sufferers in Situbondo Regency. However, there is no significant effect between the length of treatment on the success of TB treatment in Situbondo Regency.

There is a significant indirect influence between knowledge, attitudes, drug side effects, family support and medication supervisors on the success of treatment for TB sufferers in Situbondo Regency. Also, there is no indirect influence between the length of treatment on the success of treatment for TB sufferers in Situbondo Regency.

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ETHICAL CLEARANCE

The research protocol has been approved by the health research ethics committee of the Indonesian STRADA Institute of Health Sciences with number: 001206/EC/KEPK/I/03/2024.

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CONFLICT OF INTEREST

The study has no conflicts of interest.

AUTHOR CONTRIBUTION

The author contributed to this work. The author has been involved in drafting and revising the content. The author agrees to be accountable for this work.

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Profile of Nontuberculous Mycobacteria and *Mycobacterium Tuberculosis* Detected in the Sputum of Pulmonary Tuberculosis Retreatment Patients at Dr. Soetomo General Hospital

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Abstract

Tuberculosis (TB) remains one of the leading infectious diseases worldwide. Despite global efforts to control TB, it remains a major public health issue, affecting 10.6 million people annually in 2021, with significant morbidity and mortality, particularly in resource-limited settings. Effective treatment of TB requires strict adherence to long-term medication, but challenges such as treatment failure, relapse, and loss to follow-up complicate outcomes. This is especially concerning for patients with comorbidities such as diabetes, HIV, or hypertension, which not only increase the risk of TB but also hinder its treatment and elevate the likelihood of nontuberculous mycobacteria (NTM) infections. This study aimed to analyze 326 pulmonary TB retreatment cases at Dr. Soetomo General Academic Hospital from October 2023 to April 2024. The retrospective design identified that 323 cases involved MTB and 3 involved NTM. The findings show that loss to follow-up was the most common reason for retreatment, particularly among males and older adults. Comorbidities were found to exacerbate treatment challenges, with some retreatment cases lasting up to 24 months. The study concludes that loss to follow-up remains a major risk factor for TB retreatment, particularly in MTB cases, and highlights the importance of managing comorbidities to improve treatment outcomes.

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INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), remains one of the most critical public health issues worldwide.[1] In 2021, the World Health Organization (WHO) reported 10.6 million TB cases globally, with 969,000 cases occurring in Indonesia, marking an increase from 2020's estimate of 10 million cases. TB treatment requires strict adherence to a long-term regimen of antituberculosis drugs, and any interruptions in treatment can lead to complications such as treatment failure, relapse, or loss to follow-up.[2] When these outcomes occur, patients must undergo retreatment to achieve complete bacterial eradication. In 2021, the treatment success rate (TSR) in East Java was 89.13%, indicating that 10.87% of cases still required retreatment.[3]

Comorbid conditions such as HIV, malignancies, diabetes, and other chronic diseases further complicate TB treatment by weakening the immune system. HIV-1 targets CD4+ T cells and macrophages, while *Mycobacterium tuberculosis* mainly impacts macrophages, which rely on CD4+ T cells to help eliminate intracellular pathogens. Consequently, the decline in CD4+ T cells due to HIV-1 infection is believed to significantly contribute to the heightened risk of tuberculosis in individuals infected with HIV-1[4]. Associated mechanisms of TB and malignancy lead to a persistent and intense inflammatory response contributes to the development and advancement of cancer through various mechanisms. Multiple theories connect DNA damage in lung epithelial cells to free radical-induced harm and the sustenance of a cytokine network that is both pro-inflammatory and immunosuppressive.[5] Several biological factors can weaken the immune system and increase the risk of tuberculosis in people with diabetes (DM). High insulin levels are linked to reduced T helper 1 (Th1) immunity, lowering the T helper 1 to T helper 2 cell ratio and the interferon-gamma (IFN-γ) to interleukin-4 (IL-4) ratio. People with diabetes also have lower IFN-γ levels, which are negatively correlated with HbA1c, a blood sugar measure. Additionally, neutrophils in diabetics show decreased movement and bacteria-killing ability.[6] Studies have shown that TB patients with comorbid diabetes mellitus are ten times more likely to have poor TB treatment outcomes than people without diabetes mellitus due to diminished treatment responses. [7,8] Moreover, patients with a history of comorbidities such as chronic obstructive pulmonary disease (COPD), bronchiectasis, tumors, or immunosuppressant use are at a heightened risk of developing nontuberculous mycobacteria (NTM) infections.[9]

Nontuberculous mycobacteria (NTM) are becoming recognized as a crucial opportunistic pathogen for humans. NTM mostly affect the lungs and may lead to progressive disease in susceptible hosts, mainly in people with chronic lung diseases, including COPD, bronchiectasis, cystic fibrosis, and a history of tuberculosis.[10] The most prevalent nontuberculous mycobacterial species includes slow-growing such as *Mycobacterium avium* complex and *Mycobacterium kansasii*, as well as fast-growing such as *Mycobacterium abscessus* and *Mycobacterium chelonae*. [11]

Despite advances in TB treatment, there remains a significant gap in understanding the relationship between comorbidities, NTM infections, and treatment outcomes in TB retreatment cases. Current research has not fully explored the profile of NTM and MTB in TB retreatment patients, particularly in

Indonesia. Addressing this gap is crucial to improving treatment success rates and reducing retreatment cases.

This research provides valuable insights into the challenges faced by patients, particularly those with comorbidities like diabetes and HIV. Analyzing 326 cases revealed that loss to follow-up was the primary reason for retreatment, especially among older males. The study underscores the significant impact of comorbidities on treatment outcomes, demonstrating that effective management of these conditions is crucial for improving recovery rates in TB patients. This research highlights the need for targeted interventions to enhance treatment adherence and ultimately reduce TB-related complications.

MATERIALS AND METHODS

Population and Sample

This study utilizes a comprehensive dataset derived from secondary data, specifically the medical records of pulmonary tuberculosis (TB) retreatment patients at Dr. Soetomo General Academic Hospital, covering the period from January 2020 to March 2023. The dataset includes detailed records for patients aged 18 years and older who underwent sputum examination and met specific inclusion criteria. This approach ensures a robust and complete dataset for analysis. Cases with incomplete data were excluded to enhance the reliability and validity of the findings.

Methods

A descriptive retrospective design was employed to investigate the profiles of nontuberculous mycobacteria (NTM) and *Mycobacterium tuberculosis* (MTB) identified in the sputum samples of retreatment TB patients. Data were systematically organized and analyzed using Microsoft Excel (version 2406), facilitating a detailed breakdown of key variables, including demographic information, sputum culture results, and treatment outcomes. Statistical analyses were performed to identify trends and patterns within the patient population, allowing for a comprehensive understanding of the prevalence of NTM and MTB in the studied cohort.

RESULTS AND DISCUSSION

Table 1 shows that 28.4% of pulmonary TB cases required retreatment, largely due to relapse, treatment failure, or loss to follow-up, consistent with global studies.[12] Various factors contribute, including limited healthcare access, socioeconomic challenges, non-adherence to treatment, comorbidities like HIV or diabetes, and exogenous reinfections.[13]

The majority (99.07%) of retreated TB patients were infected by MTB, with only 0.93% by NTM, similar to findings by Limo (2016) in Kenya. NTM infections mimic MTB symptoms, such as chronic cough, fever, and weight loss, complicating diagnosis, especially in TB-endemic regions.[14] Additionally, NTM's slow growth makes diagnosis challenging.[15]

Drug resistance was found in 42.11% of the patients, presenting a significant challenge, as noted by Adé et al. (2016). The occurrence of drug resistance is often due to biological and clinical interactions, including poor compliance, and molecular mechanisms.[16,17]

Of those with NTM, 100% were drug sensitive (DS TB) patients, with previous TB history increasing susceptibility.[18] Co-infection with NTM and MTB poses a greater risk, particularly in those with pulmonary cavitation, which may act as a reservoir for NTM.[19]

Table 1. Proportion of new and retreated pulmonary TB patients, the mycobacterium, and the drug classification

	Amount	Percentage
Proportion		
TB	822	71.6
TB retreatment	326	28.4
Mycobacterium		
MTB	323	99.07
NTM	3	0.93
Drug sensitive		
MTB	187	57.89
NTM	3	100
Drug resistance		
MTB	136	42.11
NTM	0	0

The analysis of retreated pulmonary TB patients based on Table 2 reveals that the majority of cases occurred in adults aged 19-59 years, with 82.02% of MTB infections and 66.67% of NTM infections found in this age group. These findings align with prior research indicating that TB is most prevalent in individuals of productive age.[20,21] High mobility and socioeconomic factors contribute to the spread and severity of the disease, increasing both morbidity and mortality rates in this demographic.[22]

In contrast, adolescents (under 18 years old) represented only a small proportion of cases, with 0.62% for MTB and 33.33% for NTM. Risk factors like diabetes, smoking, and poor living conditions exacerbate the susceptibility of this age group to TB.[18] Meanwhile, elderly patients (over 60 years old) accounted for 17.67% of MTB infections, with no NTM cases. Elderly individuals, due to weakened immune systems and comorbidities, are particularly vulnerable to TB, leading to higher infection rates.[23]

Regarding gender, men represented 59.4% of MTB cases and 66% of NTM cases. This data are consistent with global trends, where TB and NTM infections are more prevalent in males.[24] Alcohol abuse is much higher in men than women. Furthermore, smoking is the most significant risk factor for COPD and lung cancer and is related to pulmonary TB. Overall, men smoke more than women. As a result, alcohol abuse and smoking are greater contributors to the TB disease burden in men.[25,26]

Table 2. Retreated pulmonary TB patients by age and gender

	Amount	Percentage
Age (MTB)		
Teenager (18 years)	2	0.62
Adult (19-59 years)	264	82.02
Elderly (60+ years)	57	17.67
Age (NTM)		
Teenager (18 years)	1	33.33
Adult (19-59 years)	2	66.67
Elderly (60+ years)	0	0
Gender (MTB)		
Male	192	59.4
Female	131	40.6
Gender (NTM)		
Male	2	66
Female	1	34

The data in Table 3 highlight common comorbidities in pulmonary TB patients. Diabetes mellitus affected 18.2% of MTB patients, which impairs immune function, leading to higher TB retreatment rates. This is consistent with findings from Siddiqui et al. (2016) and Tan et al. (2021), emphasizing how hyperglycemia disrupts immune responses and facilitates TB progression.[27]

Additionally, HIV/AIDS was present in 8.9% of MTB cases, a well-known risk factor due to its detrimental effect on T-cells and macrophages. Research by Mahtab and Coetzee (2017) and Tan et al. (2021) confirms that co-infection accelerates disease progression, making TB harder to control.[28] In HIV-1

infection, it targets CD4+ T cells and macrophages. Mycobacterium tuberculosis primarily impacts macrophages, which depend on CD4+ T cells to help eliminate intracellular pathogens. As a result, the decrease in CD4+ T cells due to HIV-1 infection is believed to significantly contribute to the increased risk of tuberculosis in HIV-1-infected individuals.[4] Hypertension was less common but still significant, as immune response disruptions can lead to pulmonary hypertension, supported by findings from Huamán et al. (2015) and Bhattacharyya et al. (2016). It is hypothesized that tuberculosis can lead to hypertension by triggering immune responses that impair endothelial function, increasing the risk of cardiovascular disease (CVD) and hypertension. TB may cause damage to lung tissue, affecting vascular structures and leading to conditions like vasculitis and endarteritis, which can reduce the cross-sectional area of pulmonary blood vessels and result in pulmonary hypertension. Additionally, if TB infects the kidneys, it can damage renal tissue, decrease kidney function, and impair blood pressure regulation, potentially causing hypertension.[29]

For NTM patients, comorbidities like hepatitis B and pituitary gland tumors were reported in 33% of cases. Studies by Khan et al. (2021) highlight the risks of drug-induced hepatotoxicity in co-infected patients. Tumors, meanwhile, worsen TB reactivation due to immune system suppression.[30] A persistent and intense inflammatory response contributes to the onset and advancement of cancer through various mechanisms. Multiple theories connect DNA damage in lung epithelial cells to free radical-induced harm and the establishment of a cytokine network that is both pro-inflammatory and immunosuppressive.[5] Lastly, the relationship between tumors and TB highlights a bi-directional link where both diseases facilitate each other's progression.[31]

Table 3. Comorbidities of pulmonary TB patients on retreatment

	Amount	Percentage
Comorbidities (MTB)		
Diabetes Mellitus	59	18.2
HIV	29	8.9
Hypertension	3	0.92
Comorbidities (NTM)		
Hepatitis B	1	33.33
Tumor	1	33.33

Based on Table 4, the majority of pulmonary TB patients on retreatment due to MTB faced loss to follow-up, accounting for 49.5%, followed by 37.5% experiencing treatment failure and 13% relapse. For patients with pulmonary TB caused by NTM, 60% encountered treatment failure, and 40% faced loss to follow-up, with no recorded relapses.

These findings align with research by Lin et al. (2021), who reported 15.9% loss to follow-up and 0.3% treatment failure. Additionally, research by Dedefo et al. (2019) in Ethiopia found 72.6% relapse, 19.6% treatment failure, and 7.8% loss to follow-up cases.

Table 4. TB treatment status of the patient

	Amount	Percentage
TB Status (MTB)		
Treatment failure	159	37.5
Relapse	54	13
Loss to follow up	207	49.5
TB Status (NTM)		
Treatment failure	3	60
Relapse	0	0
Loss to follow up	2	40

Loss to follow-up in tuberculosis cases can result from factors such as limited healthcare access, socioeconomic status, lack of family support, and non-compliance with treatment.[10] Risk factors for treatment failure and relapse include HIV infection, diabetes, malnutrition, and drug resistance.[32,33]

The data in Table 5 highlight that the longest duration of treatment for pulmonary TB was 24 months. Most drug sensitive (DS TB) patients had retreatment durations of either six months (45.26%) or 12 months (37.36%). For DR-TB (drug-resistant TB), most patients had retreatment durations of 11 months (56.61%) or 20 months (24.26%).

Table 5. Duration of treatment for pulmonary TB patients

	Amount	Percentage
Duration (Drug sensitive TB)		
6 months	86	45.26
7 months	9	4.73
8 months	10	5.26
9 months	1	0.52
11 months	2	1.05
12 months	71	37.36
13 months	4	2.10
15 months	1	0.52
16 months	1	0.52
18 months	2	1.05
20 months	1	0.52
22 months	1	0.52
23 months	1	0.52
Duration (Drug-resistant TB)		
6 months	1	0.73
9 months	5	3.67
10 months	9	6.61
11 months	77	56.61
16 months	1	0.73
18 months	8	5.88
20 months	33	24.26
21 months	1	0.73
24 months	1	0.73

Treatment duration varies due to the need for adjustments based on how patients respond to therapy. Soeroto et al. (2022) found that 43.08% of DR-TB patients required shorter treatments (9-11 months). But, the next research found 91.62% of patients with long-standing DR-TB needed longer treatment due to complications like culture conversion time or comorbidities such as malnutrition, HIV, and CKD. These factors significantly reduce the treatment success rate.[34]

For NTM infections caused by Mycobacterium avium complex, treatment typically includes three drugs—macrolides, ethambutol, and rifampicin—and must continue for 12 months after culture conversion.[35] These findings underline the importance of tailoring TB treatment based on specific patient factors to optimize recovery outcomes.

STRENGTH AND LIMITATION

The strength of this study lies in its focus on retreatment patients affected by *Mycobacterium tuberculosis* and nontuberculous mycobacteria, providing valuable insights into both types of infections. However, the research was limited by the inability to determine the specific NTM species, types of drug resistance, and the total number of patient fatalities.

CONCLUSIONS

The primary risk factor for retreated pulmonary tuberculosis, particularly in patients infected with MTB, is a high rate of loss to follow-up. Additionally, comorbid conditions exacerbate the outcomes, further complicating treatment success.

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ETHICAL CLEARANCE

The research protocol and use of medical record data was approved by Dr. Soetomo Surabaya General Hospital ethics committee (Ref. No.: 1459/LOE/301.4.2/IX/2023).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in relation to this study.

AUTHOR CONTRIBUTION

All authors were actively involved in the study design, drafting, and approval for publication.

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5. Canadian Dental Hygienists Association. Dental hygiene: definition and scope. Ottawa: Canadian Dental Hygienists Association; 1995.

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Standard Format for Journal Articles:

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Journal article 1-6 authors

1. Ramasamy R, Tong CK, Yip WK, Vellasamy S, Tan BC, Seow HF. Basic fibroblast growth factor modulates cell cycle of human umbilical cord-derived mesenchymal stem cells. Cell Prolif. 2012;45(2):132-9.

Journal article with more than 6 authors

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Journal article in press

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