Original Article

Profile of Pulmonary Tuberculosis After COVID-19 at Toba District, North Sumatra Province

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Abstract

Background: Worldwide cases of pulmonary tuberculosis (PTB) have significantly increased since the COVID-19 pandemic. Indonesia accounted for 6,811,818 of the 767,518,723 cases reported by the World Health Organization. While the Indonesian Ministry of Health reported 824,000 cases, the Global Tuberculosis Report in 2022 reported 10.6 million cases. The pandemic has hampered the goal of eliminating PTB globally, with cases diagnosed after COVID-19 having a 7.15-fold increased risk of contracting the illness.

Methods: This cross-sectional study was conducted using total sampling to identify the profile of patients with PTB after having COVID-19 based on age, gender, classification, and type of PTB, as well as the duration of occurrence of PTB after COVID-19. The data collected were from COVID-19 patients from 2020 to 2022, then compared with PTB data. All data were compared to ensure that COVID-19 and PTB patient data were the same.

Results: Of the 2544 patients recorded, 29 (1.1%) were infected with PTB after COVID-19 infection. The mean age of patients was 34±18.9 and was dominated by men (68.9%). Most of the cases were drug-sensitive TB (96.6%) and clinically diagnosed TB (55.2%). Age had a statistically significant association with the occurrence of TB cases after COVID-19 infection (P<0.0001). The mean time from the initial diagnosis of COVID-19 to the diagnosis of confirmed TB was approximately 203±34.3 days (6.7 months).

Conclusion: After COVID-19, patients have the potential to be infected with TB. Screening former COVID-19 patients can be one solution to finding early cases of PTB.

Keywords: after COVID-19, COVID-19, PTB, pulmonary tuberculosis

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INTRODUCTION

Pulmonary tuberculosis (PTB) is an infectious pulmonary disease that can disseminate to extrapulmonary and intrapulmonary organs; it is caused by *Mycobacterium tuberculosis* (Mtb).[1] As of now, PTB continues to be a significant global health concern. With a total of 10.6 million cases of PTB recorded through 2021, the Global Tuberculosis Report 2022 predicts that the number of PTB cases will increase by 17% worldwide. Contributing 9.2% of the total cases, Indonesia ranks second globally in terms of the highest-burden of PTB cases, following India.[2]

As reported in the Global Tuberculosis Report 2021, the number of newly diagnosed cases of PTB decreased worldwide from 7.1 million in 2019 to 5.8 million in 2020. This phenomenon transpired due to the impact of the Coronavirus Disease 2019 (COVID-19) pandemic on the reduction in global reports of newly diagnosed PTB cases.[3] At the same time, the annual escalation in the incidence of PTB cases is substantially influenced by incomplete case detection and low rates of effective treatment. In 2022, the Indonesian Ministry of Health estimated that 54.3% of PTB cases remained undetected in the country.[4]

The COVID-19 pandemic, which originated in China in late December 2019 and was characterized by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-caused pneumonia, evolved into an epidemic of respiratory illnesses. On March 2, 2020, Indonesia declared its initial case of COVID-19 infection. On March 11, 2020, the WHO declared COVID-19 to have evolved into a pandemic.[5]

Pulmonary TB has been affected in numerous ways by the COVID-19 pandemic since its conclusion. Several case reports described individuals who were diagnosed with PTB consecutive to developing COVID-19. This is the result of the decreased immunity mechanism induced by COVID-19 infection as well as the activation of PTB.[6–9]

The number of reported PTB cases worldwide, including in Indonesia, has decreased by 14%, according to additional reports.[2] This was the result of PTB diagnostic service disruptions, diminished health service capacity to continue PTB services, and low patient compliance with treatment. Particularly detrimental for the broader community is the fact that PTB is endemic in Indonesia, a region where the disease appears to be declining despite the observation that PTB cases are on the decline. This circumstance will also have an impact on the effectiveness of initiatives to eradicate TB, including the Indonesian Ministry of Health's National Strategy for Tuberculosis Control and the End TB Strategy 2025 of the WHO.[10]

After COVID-19 repercussions have also led to the emergence of overlapping cases of PTB worldwide, including in Indonesia. At this time, the incidence of PTB after COVID-19 is a matter of concern for several PTB-endemic nations, particularly those with low and middle-income levels. Despite this, the incidence of PTB in these population groups has been the subject of few investigations.[11,12]

A study from hospital-wide in South Africa revealed a co-infection rate of 1.5% between COVID-19 and PTB, as well as a 3-fold rise in PTB prevalence among COVID-19 patients relative to the general population. However, the order of infection that transpired initially between COVID-19 and PTB remains unexplained, thereby potentially introducing diagnostic bias into these results.[13] An additional study taken out in Thailand in 2023 reported that among the 4.2 million cases that arose after COVID-19, the possibility of developing PTB increased by 7.15-fold.[14]

Since 2020, the increase in PTB cases in Indonesia has significantly affected every province and district/city. PTB cases peaked sequentially in the provinces of West Java, East Java, Central Java, North Sumatra, and Jakarta in 2022, based on the Ministry of Health. The province of North Sumatra, which has five of the highest case counts in Indonesia, enticed scientists to conduct research in the Toba District.[15,16]

Toba Regency, the principal investigator's native region, is one of the most visited regions in Indonesia, and each community has easy access to communication; therefore, there is the unwitting possibility that active PTB infections could be transmitted. This aligns with the findings of the Toba District Health Office Report, which indicates that the intended number of PTB cases among the general population has never been identified. In the three years since the COVID-19 pandemic, the actual number of PTB cases identified has been estimated to be between 32 and 34%, falling short of the predetermined 90% target.[16]

The government of Toba Regency faces a challenge in the form of a low rate of PTB case detections. In addition, it is crucial to consider the prospective risk of developing PTB after COVID-19 as an additional priority scale for screening PTB cases as a risk group. This study's findings may serve as a point of reference for the government as it pertains to a new regulation designed to increase the success rate of targeted case findings in Indonesia, including in the Toba District.

METHOD

The research methodology employed was cross-sectional descriptive research. From 2020 to 2022, the study population comprised all data collected on patients who received COVID-19. The sampling method was conducted by total sampling based on inclusion and exclusion criteria. The first data collected was data on all COVID-19 patients from 2020 to 2022 from the Toba District Health Office. The data recapitulated were the patient's name, National ID number, date of treatment until COVID-19 recovery, and identifying the co-infection status of PTB at the time of COVID-19.

All data was checked by using the Tuberculosis Information System application of the Toba District

Health Office with the National ID number of patients to make sure that the patient had PTB after COVID-19 recovery. Data found to have PTB after COVID-19 recovery were classified again based on age, gender, classification, and type of PTB. Calculations were then made from the last date of COVID-19 recovery until the date of diagnosis of PTB as the duration of the development of PTB after COVID-19.

The inclusion criteria consisted of Tuberculosis Information System data on COVID-19 patients diagnosed with PTB after COVID-19. As study samples, patient data involving co-infection with PTB were excluded. This study has passed the Ethical Clearance of the Ethics Committee of the Faculty of Medicine, Universitas Riau, which was conducted on September 15, 2023, with Number: B/142/UN/19.5.1.1.8/UEPKK/2023.

RESULT

In 2020 and 2022, a total of 2544 patients who were diagnosed with COVID-19 comprised the study population. The data presented in Table 1 indicates that the mean age of patients diagnosed with COVID-19 was 34±18.9 years, with females comprising 60.1% of the affected population. The resulting sample consisted of 29 individuals who developed PTB after COVID-19, representing 1.1% of the overall COVID-19 patient population from 2020 to 2022. The population data was subsequently entered into the Tuberculosis Information System of the Toba District Health Office.

Table 1. Distribution of the frequencies of COVID-19 (n=2544)

Variable	N	%
Age (mean±SD)	34±18.9	
Gender		
Male	1014	39.9%
Female	1530	60.1%
Pulmonary Tuberculosis		
Yes	29	1.1%
No	2515	98.9%

Table 2 shows that among the 29 individuals who acquired PTB after developing COVID-19, about 20 (68.9%) were male patients. The patients who were subsequently classified with drug-sensitive TB (DS-TB) amounted to 28 individuals or 96.6% of the overall PTB cases. Furthermore, one participant (3.4%) in this study developed drug-resistant TB (DR-TB) after contracting COVID-19. This study also explained that the mean duration of occurrence of PTB was about 203 days after COVID-19.

Table 2. Distribution of the frequencies of PTB after COVID-19

Variable	N	%
Gender		
Male	20	68.9%
Female	9	31.1%
Classification of PTB		
DS-TB	28	96.6%
DR-TB	1	3.4%
Diagnosis of PTB		
Bacteriological	13	44.8%
Clinical	16	55.2%
Duration of PTB after COVID-19 (mean±SD)	203±34.3	

Table 3 shows the findings for the bivariate test of gender and age on the prevalence of PTB after COVID-19. The test took account of the classification of PTB, the type of PTB diagnosis, and the length of time that PTB occurs after contracting COVID-19. These findings indicated that nine samples were female and twenty were male of the 29 overall PTB after COVID-19 patients. A substantial difference (P<0.002) was found in the statistical results, with OR=0.294 (95% CI=0.133-0.648). This demonstrates that gender is a protective factor against this occurrence and that both male and female gender influence the incidence of PTB following COVID-19 instances. Thus, it could be said that the incidence of PTB following COVID-19 is only influenced by gender in 0.294 of cases.

Furthermore, of the 20 individuals who were male, 12 (60%) had bacteriological PTB and 8 (40%) had clinical PTB, according to bivariate analyses of gender variables on the type of PTB. Out of the nine female subjects, only one individual (11.1%) had PTB based on the findings of a bacteriological test, while eight (88.9%) had PTB clinically. With OR=12 (95% CI=1.2-115), the statistical findings revealed a significant difference (P<0.02). This demonstrates how gender influences the type of PTB after COVID-19, with gender acting as a protective factor during this incident.

Table 3. Bivariate Analysis for the Variable of Gender

Variable	Gender		*P*	OR (95% CI)
	Male	Female		
Pulmonary Tuberculosis				
Yes	20 (1.2%)	9 (1.89%)	0.002	0.294 (0.133 – 0.648)
No	1521 (98.8%)	994 (98.11%)		
Classification of PTB				
DS-TB	19 (95%)	9 (100%)	1.0	0.9 (0.8 – 1)
DR-TB	1 (5%)	0 (0%)		
Diagnosis of PTB				
Bacteriological	12 (60%)	1 (11.1%)	0.02	12 (1.2 – 115)
Clinical	8 (40%)	8 (88.9%)		
Duration of PTB After COVID-19	-	-	0.437	-

Based on the type of PTB diagnosis, it may be determined that gender influences PTB occurrence only 12 times after COVID-19. A significant difference (*P*<0.0001) was found in the statistical results of the bivariate test based on age. This demonstrates how age influences PTB incidence after COVID-19, with age being considered a protective factor in this investigation as well. Age and gender are characteristics that can be utilized as markers of suspicion of PTB occurrence after COVID-19 to be employed as a risk group, according to the bivariate test results overall.

Table 4. Bivariate Analysis for the Variable of Age

Variable of Age	*P*
Pulmonary Tuberculosis	<0.0001
Classification of PTB	0.819
Diagnosis of PTB	0.289
Duration of PTB after COVID-19	0.788

DISCUSSION

Since 2019, the COVID-19 pandemic issue has been inextricably linked to the rise of PTB cases worldwide. According to the Global Tuberculosis Report 2021, there was an 18% decrease in PTB incidence from 7.1 million cases in 2019–2020 to 5.8 million cases in 2020.[3] In 2021, the Ministry of Health released a report using the same data, indicating a 14% decline in PTB cases in Indonesia. After India, this decline was the second biggest in the world.[3,4]

According to reports in 2020, the detection of PTB cases fell short of the 80% target by 42%.[17] The decline in new cases of PTB caused by the COVID-19 pandemic can be attributed to various factors. These include: (1) reduced accessibility to PTB diagnosis services; (2) diminished capacity of health services to sustain therapy; (3) decreased patient inclination to seek health services amidst the COVID-19 pandemic; (4) utilization of Gen-Xpert for COVID-19 diagnostics; and (5) reallocation of budgets and resources from PTB services to countermeasures against COVID-19.[4,17]

The Global Tuberculosis Report for 2022 indicates a 9.2% increase in PTB cases from the previous year's total of 819.000 patients (2020) to 969.000 in 2022. The incidence of PTB has escalated in many countries, including India and China, in addition to Indonesia, since the release of COVID-19.[2]

As an outcome of screening for newly diagnosed cases of PTB during the COVID-19 pandemic, this problem developed. This is due to "time lags" in the increase of PTB transmission during the COVID-19 pandemic caused by misdiagnosed and untreated patients who developed PTB.[2,17] It is also worth noting that patients diagnosed with PTB often exhibit complications, which can lead to an unfavorable prognosis, which is another aspect of "time lags." The transmission of PTB to the family and adjacent environment is an additional detrimental consequence, as individuals remain unaware of their infection status and the source of transmission remains unknown.[2,17]

According to the PTB Annual Report from the Toba District Health Office in 2020–2022, the new cases found were 236, 220, and 287 cases for each year, respectively. This result was inconsistent with the annual target of 80% of 775 cases each year. This report explained that the coverage of new case findings realized from 2020-2022 ranged from 30 to 34% of the established target. Based on the results of this study, there were 29 people diagnosed with PTB

after COVID-19 from 2020-2022, with the details of 1 case in 2020, 15 cases in 2021, and 13 cases in 2022. This explains that new cases of PTB after COVID-19 contribute an estimated annual average of 3.91% to the coverage of new cases of PTB in Toba District.[16]

COVID-19 is an infectious disease that develops from SARS-CoV-2, an organism belonging to the Beta Coronaviridae family. Its specific site of infection is the lung.[18] The three stages of clinical manifestations comprise the immunopathogenesis process of COVID-19: (1) stage 1, that is an asymptomatic incubation period with or without detectable virus; (2) stage 2, that is a period of non-severe symptoms with detectable virus; and (3) stage 3, that is characterized by severe respiratory symptoms with a high viral load.[19] The interrelation between the three processes and the immune response of the body is shown through the clinical progression from multi-organ dysfunction to extensive lung injury to respiratory failure that may demand invasive mechanical ventilation.[20]

A study provides pathophysiological evidence that the severity of COVID-19 is influenced by an augmentation in the adaptive immune response mediated by CD4+ T lymphocytes, CD8+ T cells, and B cells in opposition to SARS-CoV. A diminished adaptive immune response will influence the degree of severity exhibited by COVID-19. The outcome of the specific function of CD4+ and CD8+ T lymphocytes in combating SARS-CoV-2 infection, this immune response is considered protective. Both have the potential to function as neutralizing antibodies and operate as a form of bodily compensation against infection with SARS-CoV-2.[21]

Accelerated activation of CD4+ and CD+8 lymphocytes into T-helper (Th) 1 cells, which generate Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), will enhance the efficacy of SARS-CoV-2 virus elimination. All activated pro-inflammatory cytokines will then accelerate the inflammatory process by inducing CD14+ and CD16+ monocytes with high IL-6 expression.[22]

A few more studies have demonstrated that T cells, and CD8+ T cells in particular, are crucial in the body's defense against PTB infection. The findings of these investigations elucidate that the number of CD8+ cells decreases significantly throughout the SARS-CoV-2 infection process. COVID-19 severity relates to the decrease in CD4+ and CD8+ cells that occurs during the early stages of SARS-CoV-2 infection in a dose-response fashion. COVID-19 severity is used as a proxy for the number of T cells that influence clinical manifestations.[23,24]

The body's response to COVID-19 can cause an overactive immune response, which can decrease the number and effectiveness of T-cells, increasing the risk of Mtb infection progressing to active PTB. However, patients with mild or no symptoms of COVID-19 usually have a balanced immune response, which is sufficient to maintain a healthy immune activity.[14]

Furthermore, according to a study in China, 73.6% of patients inflicted with COVID-19 regained their T cell counts within 30 days, whereas 26.4% underwent a gradual decline in T cell levels. An instance of active PTB risk can be facilitated by a reduction in the quantity of T cells, which leads to a decline in the adaptive immune response. Despite the healing process, there is a high potential risk of developing PTB following COVID-19, according to these findings.[25]

PTB and COVID-19 have a variety of clinical characteristics, including cough, fever, and shortness of breath. If not carefully examined and diagnostically furthered, this frequently results in misdiagnosis. The study by Sarinoglu et al found patients with confirmed COVID-19 and PTB simultaneously, as well as COVID-19 patients with a final diagnosis of PTB with HIV.[9]

According to the study conducted by Khayat et al, a patient experienced fever, coughing, and myalgia for three days. Reverse Transcription Polymerase Chain Reaction (RT-PCR) results verified the diagnosis of COVID-19. The patient returned seven weeks later complaining of fever, dyspnea, and chest pain. A superior lobe dextra consolidation was found after the patient's microbiologic confirmation using PTB. Due to COVID-19's propensity to produce lymphopenia, PTB often

occurs with an incidence of COVID-19. Decreased lymphocyte counts, particularly those of CD4+ cells, are correlated with increased COVID-19 severity.[9]

According to the study's findings, 29 individuals (1.1%) received a PTB diagnosis following COVID-19. One person (3.4%) out of the 29 had DR-TB incidence. This finding is not as significant as that of the Kumwichar et al study, which obtained 9.24% of PTB following COVID-19. However, according to the findings of the Thai study, there was a 7.15-fold increase in the incidence of PTB. In this investigation, the odds ratio was not calculated when COVID-19 was acquired.[14]

A hospital-based study in South Africa reported 1.5% COVID-19/PTB co-infection among patients with COVID-19.[13] These findings showed a 3-fold rise in PTB patients relative to the overall population.[3,13] These findings, however, did not explain the sequence of initial infection between PTB and SARS-CoV-2, indicating the possibility of diagnostic bias and the necessity for additional cohort study. The limited number of samples and not having direct screening of the complete population could be partially to blame for some of the differences between the two studies.[13,14]

The study's findings pointed out a variety of characteristics that could make for recommendations for PTB screening in individuals with a history of COVID-19. Gender and age are variables that can be used as indicators for screening for PTB in individuals with a previous history of COVID-19. Male gender tends to be associated with several risk factors for PTB, such as smoking, exposure to the work environment, and strenuous activity.[2,17] The results explained that there was a significant relationship between gender and the occurrence of PTB after COVID-19 (P=0.002).

Additionally, the age factor is related to the epidemiology of PTB cases, which is more prevalent in the productive age group.[17] The results of this study explain that individuals with an average age of 34 years have a significant relationship with the occurrence of PTB after COVID-19 (P<0.0001). Therefore, it can be concluded that individuals who have a history of COVID-19 with male gender and an average age of 34 years can be considered for PTB screening.

Along with these two characteristics, the statistical findings also indicate a significant correlation with the type of diagnosis of PTB that manifests, with 55.2% of the entire group having a clinical diagnosis of PTB. These findings suggest that even though PTB and COVID-19 share some clinical characteristics, PTB may still be diagnosed with certainty using supportive tests that involve microbiological and radiological.

LIMITATIONS

This study had limitations in the fact that it was conducted in one area where PTB was uncommon. Additionally, the results from this study do not apply to other studies due to the limited sample size. Given the absence of studies on PTB after COVID-19, it is anticipated that this study will inspire more studies into the potential presence of PTB after COVID-19, thereby contributing to the development of novel regulations involving early PTB screening.

CONCLUSION

PTB may develop both clinically and bacteriologically following COVID-19 infection. A history of COVID-19 should also be taken into account as a risk group for PTB. It is imperative to take note of this to concentrate and broaden the scope of PTB case discovery worldwide, particularly in Indonesia. One method for identifying early PTB cases is to examine people who have a history of COVID-19.

Additionally, depending on the type of PTB experienced, the male gender variable also influences the occurrence of PTB. The mean duration of 203±34.3 days of PTB incidence after COVID-19 can be considered as an additional or supporting indicator, but it is not statistically significant.

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