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Case Study

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Respiratory tract fungi in tuberculosis patient: A case study in Palembang Public Health laboratory center

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Abstract: Tuberculosis (TB)**,** caused by *Mycobacterium tuberculosis*, is a primarily pulmonary infectious disease spread via airborne transmission when individuals with active TB cough, talk, or sneeze. Despite longstanding TB control efforts in Indonesia, the incidence remains high, with approximately 845,000 cases annually. Prolonged use of anti-TB drugs or treatments for multidrug-resistant TB (MDR-TB), which often include immunosuppressive agents, can predispose patients to fungal infections. These infections may occur early in the disease course but are often overlooked, leading to prolonged recovery due to fungal coinfections. This study aimed to analyze the characteristics of TB patients by age, gender, and type of fungi, and to examine the relationship between fungal types and sputum characteristics (color, viscosity, and presence of blood). Using a cross-sectional design, 98 sputum samples were collected through accidental sampling. Among patients, 81 (82.7%) were adults, and 63 (64.3%) were male. Fungal analysis revealed *Candida* sp. in 41 (41.9%) samples, *Aspergillus* sp. in 9 (9.1%), mixed fungal infections in 17 (17.3%), and no fungi in 31 (31.7%). No significant association was found between fungal type and sputum characteristics (mucopurulent color, viscosity, and hemoptysis). The absence of a significant association between fungal type and sputum characteristics suggests that clinical features alone may not reliably indicate fungal coinfections in TB patients. This highlights the need for routine laboratory-based fungal diagnostics to ensure early detection and appropriate management, thereby improving treatment outcomes.

Keywords: Tuberculosis; Fungal coinfections; Multidrug-resistant TB (MDR-TB); Sputum characteristics; Laboratory-based diagnostics

INTRODUCTION

Tuberculosis remains one of the world's deadliest infectious diseases. Pulmonary tuberculosis (TB) has long been associated with opportunistic fungal infections and can be fatal if the fungal infection is not detected in the early stages of tuberculosis.[1] Every day, more than 4,100 people are reported to die of TB and nearly 28,000 people are infected with this preventable and curable disease. Global efforts to combat TB have saved an estimated 66 million lives since 2000. However, the COVID-19 pandemic has reversed years of progress made in the fight to eliminate TB. For the first time in more than a decade, the number of deaths from TB increased in 2020.[2]

The estimated total number of people infected with TB is approximately 845,000 cases with a death rate of 98,000 or equivalent to 11 deaths per hour. TB control has been implemented for more than 70 years in Indonesia, but it still ranks the highest in the world. An estimated 24,000 cases of all new tuberculosis patients are multidrug-resistant TB (MDR-TB); Historical case series of MDR-TB have shown a high frequency of cavitation and a poor prognosis. The diagnosis of chronic pulmonary aspergillosis (CPA) relies on elevated levels of Aspergillus IgG

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and Histoplasma IgG antibodies which were suspiciously detected for chronic pulmonary histoplasmosis (CPH).[3]

In 2022, the Ministry of Health together with all health workers successfully detected more than 700 thousand cases of TB. This is the highest number of findings since it became a national priority program. Based on the Global TB Report in 2022, the highest number of TB cases in the world are found in the productive age group, especially those aged 25 to 34 years. In Indonesia, the highest number of cases are found in the productive age group, especially those aged 45 to 54 years.

Long-term TB treatment with anti-TB drugs or Multidrug-resistant Tuberculosis (MDR-TB) can cause fungal infections.[4] Fungal infections can occur in earlier stages of the disease, but the patients are only given anti-TB drugs. It takes a longer time for patients to recover due to fungal co-infection.[5] In conditions of weakened immunity caused by tuberculosis, one type of fungus that can infect TB patients is *Candida albicans*. It is a normal flora in the oral cavity that turns into a pathogen and it can cause a fungal infection called oral candidiasis. Fungal infections in the lungs are relatively common in patients with weakened immune systems. Often, this infection presents clinically as a fungal ball called mycetoma.[6]

Fungal balls caused by *Aspergillus* species are a rare clinical presentation and are characterized by fungal clumps in tissue, usually in the lungs or sinuses, which end in chronic inflammation and hemoptysis. Primary aspergilloma is rarely reported because this infection mostly occurs secondary to tuberculosis infection in a pre-existing cavity. The coexistence of Aspergillus fungal balls in active tuberculosis is very rare to find.[7] Despite advancements in TB management, the interplay between tuberculosis and opportunistic fungal infections remains underexplored. The study highlights a high prevalence of fungal infections, such as *Candida* sp. and *Aspergillus* sp., among TB patients.

MATERIAL AND METHOD

This study employed an analytical research design with an observational cross-sectional approach. The population consisted of 98 sputum samples collected from tuberculosis (TB) patients. The sampling technique utilized was accidental sampling. Primary data were obtained directly from the source through laboratory examination results, collected and analyzed by the researchers. The data collection method involved analyzing respiratory tract fungi in TB patients by inoculating sputum samples onto Sabouraud Dextrose Agar (SDA) media and observing the cultures.

The data collection instrument used in this study was direct microscopic observation. Univariate analysis was conducted to examine individual variables independently, without assessing relationships between them, to describe the characteristics of each research variable. Categorical data were presented as frequency distributions, highlighting the percentage for each variable. Bivariate analysis was performed to explore the relationship between two variables: the independent variable (tuberculosis) and the dependent variables, namely sputum color (mucopurulent), consistency (viscosity), and presence of blood (hemoptysis). The data, which were nominal and ordinal in nature, were analyzed using the chi-square test to determine any statistically significant relationships.

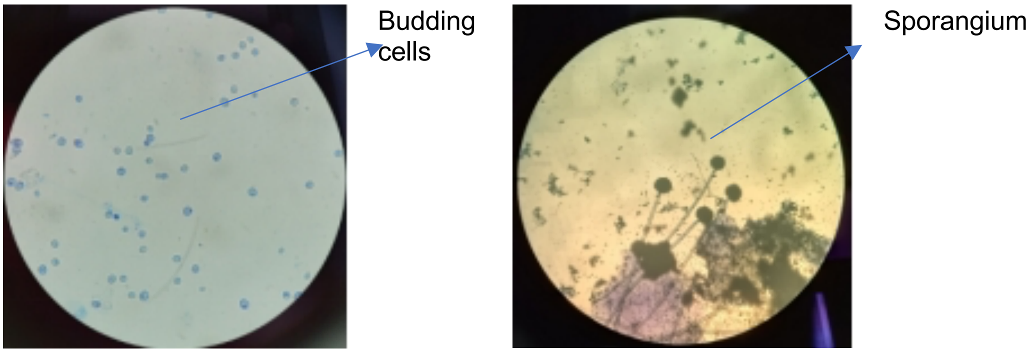
Although this study adhered to rigorous procedures, the sampling technique presented limitations, particularly regarding representativeness and potential bias. To ensure data quality and minimize contamination, sputum samples were collected under strict protocols. Patients were instructed to collect sputum in the morning immediately after waking up, to reduce contamination from saliva or nasopharyngeal secretions. The samples were collected in wide-mouthed glass containers with sterile screw caps, sterilized using a dry heat oven at 160°C for 2 hours, as prepared by laboratory personnel.

The collection process followed standard operating procedures (SOPs), supervised by laboratory personnel to ensure compliance. Samples were either analyzed immediately or stored under appropriate conditions to maintain integrity, with storage temperatures maintained at 2–8°C during transportation to the laboratory. Data analysis was conducted in two stages. First, univariate analysis was used to describe the frequency distribution of each variable. Next, bivariate analysis was performed using the chi-square test in the SPSS program to determine correlations between sputum characteristics (color, consistency, and hemoptysis) and the presence of respiratory tract fungi.

This study received ethical approval from the Health Research Ethics Committee (Institutional Review Board/IRB) of the Health Polytechnic of Palembang (Approval Number: 0947/KEPK/Adm2/VII/2024). All participants provided informed consent after receiving clear and comprehensive information about the study.

RESULTS AND DISCUSSION

The results of observations and identification of fungi in the respiratory tract of tuberculosis patients using a microscope show that *Candida albicans* is present in the initial cells and *Aspergillus* is shown by round conidia, sporangia with long and cylindrical conidiophores as in Figure 1.



Candida albicans **(a)** Aspergillus sp **(b)**

Figure 1. Fungi in respiratory tract of tuberculosis patients.

The first image (a) illustrates *Candida albicans*, a yeast-like fungus commonly found as part of the normal flora in the oral cavity, gastrointestinal tract, and vaginal mucosa. Under certain conditions, such as weakened immunity, *C. albicans* can become pathogenic, causing infections like oral candidiasis or invasive candidiasis. The image shows the characteristic budding cells of *C. albicans*, which reproduce through a process called budding, where a daughter cell forms and detaches from the mother cell. The second image (b) depicts *Aspergillus* sp., a filamentous fungus widely found in the environment, particularly in soil, compost, and decaying vegetation. The structure shown in the image is the sporangium, which contains spores that can become airborne and serve as a primary route of infection. In immunocompromised individuals, such as those undergoing long-term TB treatment, *Aspergillus* sp. can cause pulmonary aspergillosis or aspergilloma (fungal balls), particularly in pre-existing lung cavities caused by tuberculosis. These images emphasize the importance of identifying fungal pathogens through microscopic examination to ensure accurate diagnosis and effective management of fungal coinfections in tuberculosis patients.

The image (fig 2) depicts *Candida albicans* colonies grown on CHROMagar medium, which exhibit a characteristic tosca green color. CHROMagar is a selective chromogenic culture medium specifically designed for the detection, differentiation, and identification of *Candida* species. The medium contains chromogenic substrates that react with enzymes unique to each *Candida* species, resulting in distinctive colony colors that facilitate rapid identification. The tosca green coloration in the image confirms the presence of *C. albicans*, highlighting its enzyme activity specific to this species. This method is widely used in microbiological diagnostics due to its simplicity, efficiency, and ability to simultaneously differentiate multiple *Candida* species.

Figure 2. Chrom agar media

The graphs (fig 3) depict the distribution of respondents based on age and gender. In the first graph, the majority of respondents, 81 individuals (82.7%), fall within the adult age group (19–59 years), while 17 respondents (17.3%) are classified as elderly (≥60 years). This indicates that the study primarily involved participants in the productive age group, reflecting the population most affected by tuberculosis in many settings. The second graph shows the gender distribution of respondents. Males constitute the majority, with 63 individuals (64.3%), compared to 35 females (35.7%). This aligns with the known epidemiological trend where tuberculosis is more prevalent among males, possibly due to differences in exposure, health-seeking behavior, or biological susceptibility. These demographic characteristics provide a context for understanding the population most affected by tuberculosis and potentially fungal coinfections.

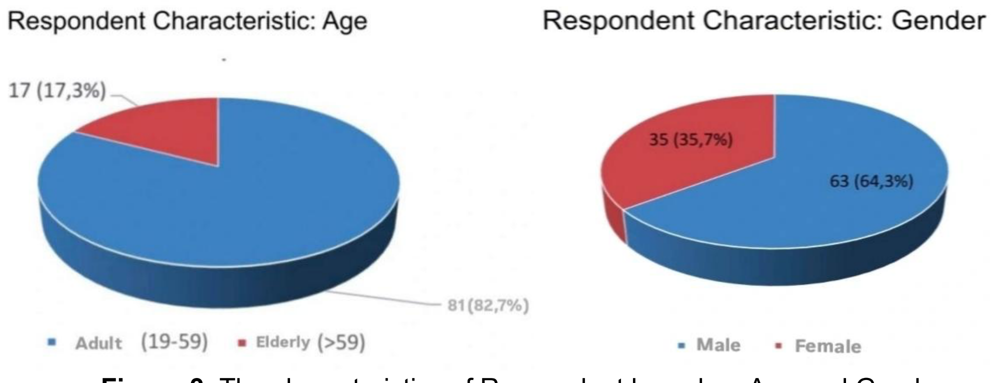


Figure 3. The characteristics of Respondent based on Age and Gender

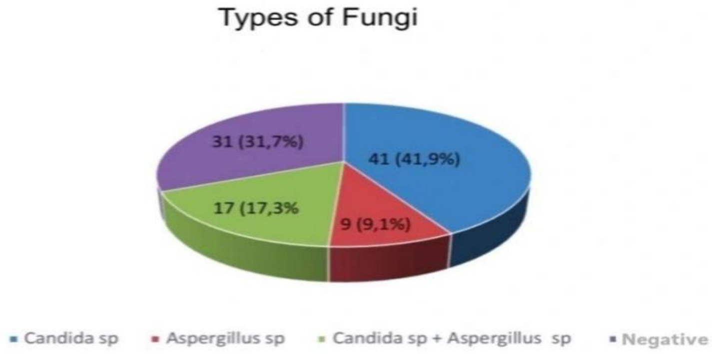


Figure 4. The types of fungi

Based on Figure 4, 41 respondents (41.9%) were infected with *Candida* sp., 9 respondents (9.1%) were infected with *Aspergillus* sp., 17 respondents (17.3%) had mixed infections, and 31 respondents (31.7%) showed no fungal infection. These findings are consistent with previous research. One study reported that 64% of children and 57.1% of teenagers were positive for fungal infections. Additionally, 46.7% of males and 56.7% of females tested positive. Another study found that, among 42 respondents, 16 were positive for *Candida* spp., including 11 respondents aged >55 years and 12 females who tested positive. Similarly, research indicated that 7 (20%) male adult samples were at risk of being infected with *Candida* spp., with 6 (17.1%) respondents aged 29–33 years and 1 (2.8%) respondent aged 40–45 years testing positive. Among females, 3 (8.5%) adult samples aged 46–51 years tested positive for *Candida* spp. These findings highlight age and gender as potential risk factors for fungal infections among tuberculosis patients.

Table 1. Distribution of respiratory tract fungi in tuberculosis patients based on sputum color (Mucopurulent)

Color	Results						P-value
	Positive		Negative		Total		
	Freq	Percentage	Freq	Percentage	Freq	Percentage	
White/Colorless	34	72.3	13	27.7	47	100	0.585
Greenish-yellow	28	62.2	17	37.8	45	100	
Brownish-red	4	66.7	2	33.3	6	100	
Total	66	67.3	32	32.7	98	100	

Based on table 1, from white/colorless sputum, 34 (72.3%) samples were found positive and 13 (27.7%) samples were negative; from greenish-yellow, 28 (62.2%) samples were found positive and 17 (37.8%) samples were negative; from brownish-red, 4 (66.7%) samples were found positive and 2 (33.3%) samples were negative. The total number of positive samples was 66 (67.3%), and negative was 32 (32.7%). From the results of the statistical analysis, the p-value was 0.585. It indicated that there was no significant relationship between the respiratory tract fungi and the color of sputum (mucopurulent), and there was no significant relationship in terms of the color of the fungi growing in the media.

The results of the analysis showed that there was no significant relationship between the presence of fungi in the respiratory tract of tuberculosis patients and the color of mucopurulent sputum (p-value = 0.585). This finding is consistent with several kinds of literature such as in [10] stating that sputum color alone is often not enough to be a specific indicator of fungal or bacterial infection in tuberculosis patients. Sputum analysis is more often used to detect *Mycobacterium tuberculosis* with methods such as microscopic examination, sputum culture (gold standard), or molecular rapid tests (GeneXpert MTB/RIF). Visual examination of sputum, including color, is usually only used to assess sample quality but not for specific diagnosis of fungal infection.[11]

Table 2. Distribution of respiratory tract fungi in tuberculosis patients based on consistency (Viscosity)

Consistency (Viscosity)	Results						P value
	Positive		Negative		Total		
	Freq	Percentage	Freq	Percentage	Freq	Percentage	
Thick	63	67.0	31	33.0	94	100	0.605
Not thick	3	75.0	1	25.0	4	100	
Total	66	67.3	32	32.7	98	100	

Based on Table 2, from thick sputum, 63 (67.0%) samples were found positive, and 31 (33.0%) samples were negative; from not thick samples, 3 (75.0%) samples were positive and 1 (25.0%) sample was negative. After being analyzed, the results of the p-value were 0.605, meaning there was no significant relationship between the respiratory tract fungi of tuberculosis patients and consistency (viscosity). In terms of thickness (viscosity) the fungi growing in the media did not show a significant relationship. From the results of the study on the relationship between sputum viscosity and fungal detection in patients with pulmonary tuberculosis (TB), it was found that there was no significant relationship (p-value = 0.605). This shows that the sputum viscosity factor, whether thick or not, is not the main indicator that influences the presence of fungi in the respiratory tract of TB patients. Several other literatures also confirm that the presence of fungi is more influenced by the patient's immunodeficiency condition and environmental exposure to fungal spores.[12]

In general, fungal infections often occur in TB patients due to a decreased immune system, especially in elderly patients or those receiving long-term antibiotic treatment. A study at Soekardjo Hospital, Tasikmalaya, for example, showed that 22.2% of TB patients had fungi in their sputum, with a higher prevalence in elderly patients.[13]

Table 3. Distribution of respiratory tract fungi in tuberculosis patients based on blood presence (hemoptysis)

Blood Presence (hemoptysis)	Results						P value
	Positive		Negative		Total		
	Freq	Percentage	Freq	Percentage	Freq	Percentage	
Bleeding	5	62.5	3	37.5	8	100	0.519
Not bleeding	61	67.8	29	32.2	90	100	
Total	66	67.3	32	32.3	98	100	

Based on Table 3, from samples with blood, 5 (62.5%) samples were positive and 3 (37.5%) samples were negative; and from those with no blood, 61 (67.8.0%) samples were positive and 29 (32.2%) samples were negative. After being analyzed statistically, the result of the p-value was 0.519. It meant that there was no significant relationship between the respiratory tract fungi and the presence of blood (hemoptysis) in samples. In terms of hemoptysis, the fungus growing in the media did not show a significant relationship.

The results of table 3 showing the relationship between hemoptysis (blood in sputum) and the presence of fungi in tuberculosis patients, it was obtained that the p-value was 0.519. This meant there was no significant relationship between hemoptysis and fungal infection in the respiratory tract of tuberculosis patients.

These results can be explained by the fact that hemoptysis, or coughing up blood, is often associated with damage to lung tissue due to active TB infection, but does not directly indicate the presence of a fungal infection. Hemoptysis can occur in a variety of conditions, including bacterial infections or tuberculosis, but the presence of fungi in sputum is more often influenced by immunosuppression or co-infection factors, rather than by clinical symptoms such as hemoptysis.

Previous studies have also shown that hemoptysis in TB patients is more often related to the severity of tuberculosis infection or the presence of other comorbidities, while fungal infections tend to develop in patients with more severe immune disorders. Patients over 40 years of age were more likely to provide sputum samples contaminated with the respiratory fungi, C. albicans.[14] In sputum and tracheal aspirates, the chance of identifying one species was higher than the chance of identifying multiple species. Culture on Sabouraud Dextrose Agar (SDA) media from 103 bronchoalveolar lavage (BAL) fluid samples, there were 23 samples (22.3%) positive for Candida spp. found in men [15]

In macroscopic and microscopic examinations, the results were obtained based on the percentage of the presence of fungi in the respiratory tract of Candida sp. which grew on SDA media. The results of the study from 62 samples obtained 34 (54.9%) positive samples of Candida sp.[16] The prevalence of Candida sp respiratory tract fungus in all samples analyzed was 31.60%. After excluding contaminated samples, the actual prevalence was 27.66%. Of all sputum samples, 31.6% were contaminated.[17]

This research is in line with[18] The results of the study showed that out of 30 samples, 7 (23.3%) samples were found to be infected with Candida albicans, 8 (26.7%) samples with Candida parasilopsis II, and 15 (50%) samples were negative. This study concludes that out of 30 samples, 15 samples were detected that had the Candida spp. gene. The results of both studies showed agreement in terms of the presence of Candida infections in the respiratory tract, although the species-specific results and percentage figures were slightly different. The first study provides an overview of the prevalence of Candida in more samples, while the second study offers specific details about the types of species involved.

The overall comparison is that both results are in line in terms of showing the prevalence of Candida fungi in the respiratory tract, although there are differences in methodology and level of specification between the two studies. These differences could be caused by different sample sizes, types of species detected, and identification methods used. Thus, despite differences in specific results between the two studies, both still demonstrate significant Candida infection in the respiratory tract.[19] Candida will live in balance with other microorganisms in the body without causing harm, with approximately 15% to 30% of healthy people carrying Candida in the mouth and throat and 15% in the bronchi.[20]

However, when conditions are favorable, Candida has the opportunity to multiply and cause disease in many other parts of the body. Candida pneumonia is generally confined to severely immunocompromised patients who develop the infection after it has spread from the bloodstream to the lungs. A chest CT scan often shows multiple lung nodules.[21]Candida albicans lung disease: Fungal cases of pneumonia are a small proportion of pneumonia and Candida is the most common cause of invasive fungal infections, accounting for 70-90%. Fungi can be present in the body without causing disease or can cause significant disease, especially in immunocompromised settings.[22]

Things to note in sputum sampling color should be yellowish-green and mucoid viscosity. The best time for sputum collection is after waking up because abnormal bronchial secretions tend to collect during sleep so that the sputum is not contaminated by saliva or nasopharyngeal secretions to avoid biased results.[23]

There is no influence based on volume, but there is an influence based on the smell, color, and consistency of sputum because the condition of sputum usually specifically shows the pathological process that occurs in the formation of the sputum itself.[24] The results of this study are in line with the statement according to [25] in *Science Direct Topics* stating that normal sputum is odorless, conversely, foul-smelling sputum indicates a bacterial infection. A similar thing was explained by [26], sputum that has a foul odor is likely a sign of lung abscess or bronchiectasis. A study conducted by L.R. Bijland et all (2013) discussed the diagnosis of disease through odor in samples. The study concluded that odor detection by animals and electronic noses holds promise for the future and should receive higher priority in research and funding efforts.[27]

The ideal consistency (viscosity) of sputum for TB examination is mucoid, which is thick and slimy to facilitate proper laboratory examination.[28] Things to note in taking sputum samples must be thick, namely by spontaneous coughing, sputum induction, and bronchoscopy. There is no influence based on volume, there is an influence based on the smell, color, and consistency of sputum. If the sample does not meet the requirements, then a repeat sample can be taken, or if not possible, the most mucopurulent or thick part of the sample can be taken with a special note on the label. The sample should also not contain food residue or other solid particles.[29]

This study provides important insights into the clinical management of tuberculosis. Routine screening for respiratory tract fungal infections, especially Candida sp and Aspergillus sp, in tuberculosis patients is recommended, given the high prevalence of detected fungal infections. This screening can help identify secondary infections early and prevent complications. In addition, tuberculosis patients need to be educated about the risk factors for fungal infections, such as immunosuppression, environmental hygiene, and healthy lifestyles, as additional preventive measures[30]. It is recommended that future studies involve larger sample sizes and incorporate more diverse variables, such as environmental factors, patient immune status, and disease duration, to gain a deeper understanding of the mechanisms underlying the association between tuberculosis and fungal infection.[31] Molecular analysis for the identification of fungal species can strengthen the evidence and provide more accurate data in determining antifungal therapy strategies. In addition, this study highlights the importance of including fungal infection examinations in tuberculosis diagnostic guidelines. This can improve the quality of health services and ensure more comprehensive treatment. By applying these insights, the results of this study are expected to make a real contribution to improving the management of tuberculosis and the management of accompanying fungal infections [32].

CONCLUSION

The study, conducted on 98 sputum samples from tuberculosis patients at the Palembang Public Health Laboratory Center, concluded that the majority of patients (81, 82.7%) were adults, with a higher prevalence among males (63, 64.3%). Respiratory tract fungal infections were detected in 67 samples (68.3%), with the following distribution: *Candida* sp. in 41 samples (41.9%), *Aspergillus* sp. in 9 samples (9.1%), and mixed fungal infections in 17 samples (17.3%). Meanwhile, 31 samples (31.7%) showed no fungal growth. Statistical analysis revealed no significant relationship between fungal infections and sputum characteristics, including color (mucopurulent), consistency (viscosity), or the presence of blood (hemoptysis). These findings emphasize the importance of routine fungal diagnostics in tuberculosis patients to better understand the impact of fungal coinfections.

AUTHORS’ CONTRIBUTIONS

Herry Hermansyah: author, editor, planning and implementing the research, Sri Sulpha Siregar: revising the manuscript, preparing samples, implementing the research, and administrator, Erwin Edyansyah: corresponding author, collecting, processing and analyzing data. All authors contributed equally in every stage of the research process.

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DATA AVAILABILITY STATEMENT
The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT
The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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