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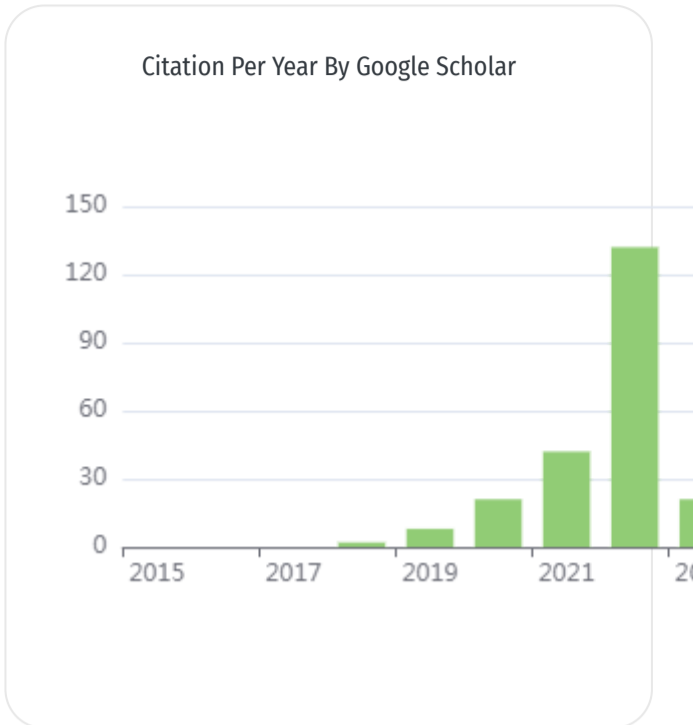
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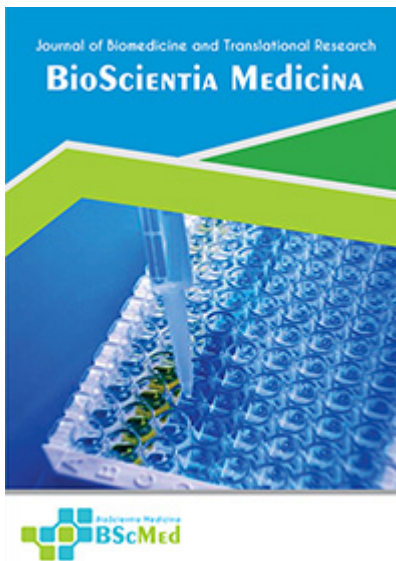
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
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
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
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
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## Bioscientia Medicina: Journal of Biomedicine & Translational Research

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### Comparison of Chest X-Ray Findings Between Primary and Secondary Multidrug Resistant Pulmonary Tuberculosis

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#### ABSTRACT

**Introduction:** Radiological imaging has a key role in multidrug-resistant (MDR) pulmonary tuberculosis (TB) screening and diagnosis. However, new cases of MDR pulmonary TB are often overlooked; therefore, its transmission might continue before its diagnosis. The most widely used and affordable radiological modality is a chest radiograph. This study aims to describe the characteristics of primary and secondary MDR pulmonary TB chest x-ray findings for differential diagnosis.

**Methods:** This study was an analytic observational study with a retrospective design. Researchers evaluated medical record data of primary and secondary MDR pulmonary TB patients who underwent chest x-ray examinations. The patient's chest x-rays were then evaluated. Evaluated variables were lung, pleural, and mediastinal abnormalities and severity category.

**Results:** The most common chest x-ray finding in primary MDR pulmonary TB was consolidation (96.2%), which was mostly unilateral (52.0%), accompanied by cavities (71.2%), most of which were multiple (83.8%) with a moderate category of severity. The most common chest x-ray finding in secondary MDR pulmonary TB was consolidation (100%), which was mostly bilateral (60.4%), accompanied by cavities (80.2%), most of which were multiple (90.1%) with severe category of severity. Pleural thickening (47.5%) was also found.

**Conclusion:** There was a significant difference between primary and secondary MDR pulmonary TB in terms of mild severity category, and pleural thickening. Mild severity category is mostly found in primary MDR-TB and pleural thickening is mostly found in secondary TB.

#### 1. Introduction

One of the global concern in tuberculosis (TB) is drug-resistant TB. One drug-resistant TB types is Multidrug-Resistant/Rifampicin Resistant TB (MDR/RR-TB). In 2018, MDR/RR TB was estimated to occur at 2.4% of new cases and 13% of previously treated cases in Indonesia. The incidence of MDR/RR-TB cases in the same year was 24,000 cases<sup>1</sup>.

Multidrug-Resistant TB is divided into primary and secondary MDR. Secondary MDR-TB refers to resistance that develops during or after  $\geq$  one month of

chemotherapy in previously drug-sensitive TB patients. Primary MDR-TB refers to resistance that develops in patients who had not received TB treatment before or received therapy for less than one month<sup>2</sup>.

Radiological imaging has a role in screening and supporting MDR pulmonary TB diagnosis. A study by Sulaiman et al. in 2018 regarding chest x-ray findings in pulmonary MDR-TB at Dr. Soetomo General Hospital, Surabaya, reported that pulmonary MDR-TB patients mostly had severe lesions, with the most

frequent finding were ground-glass opacity/consolidation with bilateral lung involvement<sup>3</sup>.

Studies regarding radiological findings of primary MDR pulmonary TB, especially those that compare it with secondary MDR pulmonary TB, are still very limited, while new cases of pulmonary MDR-TB are often overlooked, therefore its transmission might continue before its diagnosis<sup>4</sup>. The most widely used and affordable radiological modality is a chest radiograph. This study aims to describe the characteristics of primary and secondary MDR pulmonary TB chest x-ray findings for differential diagnosis purposes.

## 2. Methods

This study is an analytic observational study with a retrospective design. The study used data from primary and secondary MDR pulmonary TB patients who had undergone chest x-ray examination before starting treatment at Radiology Diagnostic Installation of Dr. Soetomo General Hospital, Surabaya, from January 2018 to December 2020.

The study sample was primary and secondary MDR pulmonary TB patients who met inclusion criteria as follows: (1) Multi-Drug Resistant pulmonary TB patients that had been confirmed by GeneXpert and anti-tuberculosis drug sensitivity tests; (2) Age  $\geq$  15 years old; (3) Chest x-ray examination results were available before starting treatment. The sample exclusion criteria were other findings on chest x-ray besides the TB process that might interfere with TB findings, such as: massive effusions, massive atelectasis, lung tumors, and extensive pneumonia outside TB.

We identified medical record data of primary and secondary MDR pulmonary TB patients who underwent chest x-ray examination. Patients who met inclusion criteria were taken as study samples. Furthermore, the sample was divided based on primary and secondary MDR pulmonary TB according to the aforementioned definition. Their chest x-ray findings were evaluated, which included lesion characteristics in abnormalities

in the lung parenchyma, pleura, and mediastinum, and severity category. The evaluated chest x-ray was a posteroanterior position chest x-ray using Hitachi Radnext50 500 mAs x-ray diagnostic device. The evaluation was conducted by a Radiologist in Thoracic Division, and the results were written on available worksheets. The data obtained were analyzed and presented as study results.

Statistical data were processed using Statistical Program Social Science (SPSS) software with independent sample t-test, Mann Whitney test, and Chi-square test for ratio-interval, ordinal, and nominal data. The error rate used was 5%.

## 3. Results

A total of 190 primary and secondary MDR pulmonary TB patients were included during the study period. Thirty-seven patients were excluded because eight people did not undergo baseline chest x-ray examination, and 29 people had incomplete medical record data. The total sample studied was 153 patients. The sample was divided into primary and secondary MDR pulmonary TB patients with 52 primary MDR pulmonary TB patients and 101 secondary MDR pulmonary TB patients.

Most primary and secondary MDR pulmonary TB samples were in the 46-55 years group based on age groups. The mean age for primary MDR pulmonary TB patients was 43 years (SD $\pm$ 14.37), while for secondary MDR pulmonary TB, the mean age was 45 years (SD $\pm$ 12.41).

Based on gender, male and female patients were equal in the primary MDR pulmonary TB group. It was found that the number of male patients was greater than female patients in secondary MDR pulmonary TB.

The comorbid factors recorded in primary and secondary MDR pulmonary TB were diabetes mellitus and HIV. Most case status of patients in this study was "in treatment" status. Complete data on basic characteristics of primary and secondary MDR pulmonary TB patients shown in Table 1.



**Table 1. Characteristics of primary and secondary MDR pulmonary TB**

<b>Characteristics</b>	<b>Primary MDR pulmonary TB</b>	<b>Secondary MDR Pulmonary TB</b>
<b>Age</b>		
15-25 years	8 (15.4%)	11 (10.9%)
26-35 years	8 (15.4%)	12 (11.9%)
36-45 years	9 (17.3%)	26 (25.7%)
46-55 years	14 (26.9%)	29 (28.7%)
56-65 years	10 (19.2%)	19 (18.8%)
66-75 years	3 (3.0%)	4 (4.0%)
Mean ± SD	43±14.37 years	45±12.41 years
<b>Gender</b>		
Male	26 (50%)	63 (58.2%)
Female	26 (50%)	38 (41.8%)
<b>Comorbid</b>		
Diabetes mellitus	8 (15.38%)	13 (12.87%)
HIV	1 (1.90%)	2 (1.98%)
<b>Case Status</b>		
In treatment	35 (67.3%)	69 (68%)
Recovered	10 (19.2%)	9 (8.9%)
Treatment discontinued	3 (5.8%)	11 (10.9%)
Deceased	4 (7.7%)	12 (11.9%)

The most common pulmonary abnormalities in chest x-ray of samples were consolidation, which was found in 96.2% of primary MDR pulmonary TB patients and all secondary MDR pulmonary TB patients. The most common lesion location in primary MDR pulmonary TB was in the upper and middle zone, while in secondary MDR pulmonary TB, the most common location was the middle and upper zone. In primary MDR pulmonary TB, most consolidation was found in unilateral lungs (52%), while in secondary MDR pulmonary TB, the majority of consolidation was found in both lungs (bilateral) in 60.4% of patients.

The pulmonary cavity was found in 71.2% of primary MDR pulmonary TB patients and 80.2% of secondary MDR pulmonary TB patients, wherein both groups most cavities were multiple cavities instead of the single cavity. Other pulmonary abnormalities were interstitial opacities, where it was found in 42.3% of primary MDR pulmonary TB patients and 45.5% of secondary MDR pulmonary TB patients. Millary pattern in this study was only found in 1 patient who belonged to the primary MDR pulmonary TB group (1.9%).

Fibrosis finding was found in the majority of patients in primary and secondary MDR pulmonary TB, with 96.2% and 98% of patients, respectively. Several pulmonary abnormalities, mostly inactive lesions other than fibrosis, were present in smaller numbers. These included calcification, atelectasis, bronchiectasis,

emphysema and destroyed lung.

Pleural abnormalities observed were pleural effusion, pleural thickening, pleural calcification, and pneumothorax. The study results on primary MDR pulmonary TB samples showed that 19.2% of patients had pleural thickening, while the percentage in secondary MDR pulmonary TB patients was 47.5%.

Mediastinal abnormalities in the chest x-ray that were observed included hilar and mediastinal lymphadenopathy and mediastinal shift. The results showed that most primary and secondary MDR pulmonary TB patients had a mediastinal shift, with 45 patients (86.5%) and 95 patients (94.1%), respectively.

Other chest x-ray findings were in the form of severity categories. These findings were assessed based on a scoring system according to Yan et al. (5). In the primary MDR pulmonary TB group, 21 patients (40.3%) fell into the severe severity category, 27 patients (52%) fell into the moderate severity category, and 4 patients (7.7%) fell into the mild severity category. In the secondary MDR pulmonary TB group, most patients fell into the severe severity category, with 60 patients (59.4%), 40 patients (39.6%) fell into the moderate severity category, and only one person (1%) fell into mild severity category. Complete data for chest x-ray findings in primary and secondary MDR pulmonary TB are outlined in Table 2.

**Table 2. Chest x-ray finding comparison between primary and secondary MDR pulmonary TB patients**

<b>Chest X-Ray Findings</b>		<b>Primary MDR-TB n = 52</b>	<b>Secondary MDR-TB n = 101</b>	<b>p value</b>
<b>Pulmonary Parenchymal Abnormalities</b>				
1	<b>Consolidation</b>	50 (96.2%)	101 (100.00%)	0.114
	Location			0.822
	Upper zone	46 (39.7%)	84 (37.3%)	
	Middle zone	46 (39.7%)	88 (39.1%)	
	Lower zone	24 (20.7%)	53 (23.6%)	
	Laterality			0.148
	Unilateral	26 (52.0%)	40 (39.6%)	
	Bilateral	24 (48.0%)	61 (60.4%)	
2	<b>Cavity</b>	37 71.2%	81 80.2%	0.207
	Number of lesions			0.364
	Single	6 (16.2%)	8 (9.9%)	
	Multiple	31 (83.8%)	73 (90.1%)	
3	<b>Interstitial opacities</b>	22 (42.3%)	46 (45.5%)	0.703
4	<b>Nodules</b>	5 (9.6%)	15 (14.9%)	0.363
	<b>Number of nodules</b>			0.260
	Single	0	6 (40%)	
	Multiple	5 (100%)	9 (60%)	
5	<b>Miliary pattern</b>	1 (1.9%)	0	0.340
6	<b>Fibrosis</b>	50 (96.2%)	99 (98%)	0.605
7	<b>Calcification</b>	2 (3.8%)	9 (8.9%)	0.334
8	<b>Emphysema</b>	10 (19.2%)	34 (33.7%)	0.062
9	<b>Bronchiectasis</b>	23 (44.2%)	39 (38.6%)	0.503
10	<b>Atelectasis</b>	10 (19.2%)	34 (33.7%)	0.062
11	<b>Pulmonary destruction</b>	2 (3.8%)	6 (5.9%)	0.717
<b>Pleural Abnormalities</b>				
12	<b>Pleural effusion</b>	7 (13.5%)	22 (21.8%)	0.214
13	<b>Pleural thickening</b>	10 (19.2%)	48 (47.5%)	0.001
14	<b>Pleural calcification</b>	0	2 (2%)	0.548
15	<b>Pneumothorax</b>	0	0	
<b>Mediastinal Abnormalities</b>				
16	<b>Hilar lymphadenopathy</b>	4 (7.7%)	7 (6.9%)	1.000
	Laterality			1.000
	Unilateral	3 (75.0%)	6 (85.7%)	
	Bilateral	1 (25.0%)	1 (14.3%)	
17	<b>Mediastinal lymphadenopathy</b>	0	0	
18	<b>Mediastinal shift</b>	45 (86.5%)	95 (94.1%)	0.133
	Location			0.330
	Trachea	11 (22.4%)	38 (38.0%)	
	Hilus	36 (73.5%)	84 (84.0%)	
	Heart	2 (4.1%)	12 (12.0%)	
<b>Severity Category</b>				
19	<b>Severity Category</b>			0.058
	Mild	4 (7.7%)	1 (1.0%)	0.046
	Moderate	23 (52.0%)	40 (39.6%)	0.582
	Severe	25 (40.3%)	60 (59.4%)	0.182

#### 4. Discussion

The ratio of primary and secondary MDR pulmonary TB in this study was 1: 2. This ratio is higher compared

primary and secondary MDR pulmonary TB ratio in a previous study by Sulaiman et al. in 2018. This finding indicates that it is necessary to expand the detection

range and coverage of MDR-TB in the future<sup>3</sup>.

The largest age group in this study was the 46-55 primary and secondary MDR pulmonary TB. The mean age of patients with primary and secondary MDR pulmonary TB was 43 and 45 years, respectively. This result is in line with a previous MDR-TB study by Sulaiman et al., where they reported MDR-TB patient's mean age of 46 years [3]. A study by Kim et al. also reported similar results. The age range in their MDR-TB patients was between 20-82 years, and the mean age was 43 years<sup>6</sup>.

Male and female patients in the primary MDR pulmonary TB group was equal, whereas male predominance was found in the secondary MDR pulmonary TB group. In a study by Rai and Alok in 2019, it was found that the majority of primary and secondary MDR pulmonary TB patients was male. Other studies by Kim et al. in 2015 and Chung et al. in 2006 also reported that most MDR pulmonary TB patients were male<sup>7,8</sup>.

In this study, 17.3% of primary MDR pulmonary TB patients had comorbid factors, while in secondary MDR pulmonary TB, the percentage was 14.9%<sup>7,8</sup>. The two most common comorbidities were diabetes mellitus and HIV/AIDS. In a study by Li et al., they reported that diabetes mellitus was comorbid in MDR-TB patients<sup>2</sup>.

One of the most common findings during chest x-ray observation was consolidation in the majority of primary and secondary MDR pulmonary TB patients (96.2% versus 100%). The most prevalent consolidation locations in primary MDR pulmonary TB were upper and middle zone, while in secondary MDR pulmonary TB, the most prevalent locations were middle and upper zone. In this study, it was known that consolidation in primary MDR pulmonary TB mainly was unilateral, while in secondary MDR pulmonary TB, it was mostly bilateral. This active lesion was the dominant lesion in primary and secondary MDR pulmonary TB besides multiple cavities and interstitial opacities.

Kim et al. in 2014 stated that consolidation was found in 90% of patients with primary resistance MDR pulmonary TB<sup>6</sup>. Kim et al. in 2015 stated that consolidation was found in 60-93% of MDR-TB cases

with secondary resistance. This suggests that consolidation is a common feature in primary and secondary resistant MDR pulmonary TB, one of the main signs of active TB infection. Most of them show extensive lesions in primary and secondary MDR pulmonary TB that affect several zones simultaneously<sup>7</sup>.

A study by Rai and Alok that compared primary and secondary MDR pulmonary TB features revealed that bilateral lesions were more frequent in secondary MDR pulmonary TB than primary MDR pulmonary TB. Some literature suggested that consolidation and cavity in MDR-TB are due to previously failed treatment or MTB mutation that eventually leads to resistance. MTB resistance results in TB reactivation and triggers it to spread more extensively, forming new consolidations and cavities<sup>4,9</sup>.

Cavity was found in most of the samples of this study. Cavities were found in 71.2% of the primary MDR pulmonary TB sample, while in secondary MDR pulmonary TB, it was found in 80.2% of the sample. Most of them were multiple cavities, both in primary MDR pulmonary TB (83.8%) and secondary MDR pulmonary TB (90.1%). Various literature stated that the cavity is a predisposing factor for TB treatment failure and anti-tuberculosis drugs resistance. The difficulty of the drugs to penetrate the avascular cavity, which contains large amounts of *Mycobacterium tuberculosis*, is believed to be the cause of resistance to anti-tuberculosis drugs. SH Kim et al. reported that cavities were found in 85% of primary MDR pulmonary TB patients<sup>6</sup>. Another study by Zahirifard et al. in 2003 showed that cavities were found in 80% of secondary MDR pulmonary TB patients<sup>10</sup>.

Interstitial opacities were quite common in this study. It was found in 42.3% and 45.5% of primary and secondary MDR pulmonary TB patients, respectively. A study by Cha et al. in 2009 that observed reticulonodular opacity feature in MDR-TB stated that reticulonodular opacity was found in 75% of primary MDR pulmonary TB patients<sup>11</sup>.

The miliary pattern was only found in a small proportion of primary MDR pulmonary TB samples. Ko et al. in 2014 stated that miliary TB is a rare

manifestation of TB<sup>12</sup>. Another study reported that the miliary features in immunocompromised patients could also be found in immunocompetent patients<sup>13</sup>.

Fibrosis feature in primary and secondary MDR pulmonary TB sample was 96.2% and 98%, respectively. This finding was higher than the results of a study by Zahirifard et al., where they reported fibrosis in 67% of MDR pulmonary TB patients. Fibrosis is formed when the disease enters a chronic phase as part of the healing and remodelling process, which involves the role of various Th2-regulated pro-fibrotic cytokines such as TNF $\alpha$ , TGF $\beta$ , IL4, and IL-13. The higher proportion of fibrosis in this study was since most patients were treated when clear clinical manifestations had appeared. Therefore, the patients had entered a chronic stage and thus gave fibrosis feature in chest x-ray<sup>10</sup>.

Several lung abnormalities, including inactive lesions, were found to be greater in secondary than primary MDR pulmonary TB. This finding aligns with the natural course of secondary MDR pulmonary TB, which undergoes reactivation and repeated reinfection with a more extended history of treatment and higher chronicity than primary MDR pulmonary TB.

Pleural abnormalities observed in this study included pleural effusion, pleural thickening and pleural calcification. Pleural effusion in secondary MDR pulmonary TB was more prevalent than primary MDR pulmonary TB. Pleural thickening features were also significantly higher in secondary MDR pulmonary TB patients than primary MDR pulmonary TB. Zahirifard et al. stated that the most prevalent pleural involvement in MDR pulmonary TB was pleural thickening (31%) [10]. A study by Uskul et al. stated that pleural thickening was associated with a delayed type of hypersensitivity reactions, tuberculous pleurisy, which is the presence of fluid in the pleural cavity due to increased adenosine deaminase activity. This condition often occurs in post-primary infections, the presence of HIV infection, and primary infections in older patients<sup>14</sup>.

Observation of mediastinal abnormalities on chest x-ray included hilar lymphadenopathy, mediastinal shift and mediastinal shift. The mediastinal shift is an

altered position of various mediastinal structures (trachea, heart, large blood vessels/hilar) due to pulmonary parenchymal or pleural fibrosis. This study showed that mediastinal shift was found in 86.5% and 94.1% of primary and secondary MDR pulmonary TB patients, respectively. Similar findings were found in a study by Icksan et al., where they reported that mediastinal shift was found in 30.1% of patients in the form of tracheal deviation and 34.9% of patients in the form of and hilar elevation<sup>9</sup>.

The severity category was assessed based on a scoring system according to Yan et al.<sup>5</sup>. In this study, 40.3% of primary MDR pulmonary TB patients were included in the severe category, 52% were in the moderate severity category, and only 7.7% were in the mild severity category. In secondary MDR pulmonary TB, 59.4% were included in the severe severity category, 39.6% were in the moderate severity category, and only 1% were in the mild severity category. A study by Rai and Alok found a significant difference in moderate lesions between primary and secondary MDR pulmonary TB<sup>4</sup>. A study by Domingo Palmero reported that 75% of MDR-TB patients showed extensive lesions on chest x-ray. This condition is believed to be related to the long duration of the disease and the more significant number of cavities and wider cavity extension in MDR-TB. The central part of the cavity that undergoes liquefaction contains a large number of bacteria and could spread to the surrounding lung parenchyma through bronchial branches; therefore, parenchymal lesions are becoming more extensive<sup>4,15</sup>.

There were several limitations in this study. This study is hospital-based study; therefore, it could not provide information regarding primary and secondary MDR pulmonary TB prevalence in the community. The study sample of secondary MDR pulmonary TB included all MDR-TB with a treatment history of  $\geq 1$  month, not specific to one treatment history.

## 5. Conclusion

Comparing chest x-ray findings on primary and secondary MDR pulmonary TB showed significant differences in terms of mild severity category and pleural thickening. Most mild cases were found in

primary MDR pulmonary TB, whereas pleural thickening was more common in secondary MDR pulmonary TB. Following the natural course of primary and secondary MDR pulmonary TB, it was found that active consolidation in secondary MDR pulmonary TB was more prevalent in the middle and upper zone, which were bilateral accompanied by multiple cavities. Most severe cases, pleural thickening, and inactive lesions were also found in secondary MDR pulmonary TB. In primary MDR pulmonary TB, there was more active consolidation in the upper and middle zone which were unilateral accompanied by multiple cavities with more moderate cases and less inactive lesions.

## 6. Acknowledgement

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## 7. Ethical Clearance

The protocol of this study was approved by the Institutional Ethics Committee, Faculty of Medicine, Airlangga University, Surabaya.

## 8. Source of Funding

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## 9. Conflict of Interest

None

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