

Original Article

THE ASSOCIATION BETWEEN WHO CLINICAL STAGE AND OTHER RISK FACTORS WITH PULMONARY TUBERCULOSIS AMONG PEOPLE LIVING WITH HIV/AIDS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Objective: To estimate the Pulmonary Tuberculosis (PTB) prevalence among the participants/People Living With HIV/AIDS (PLWHAs) and to verify the association between WHO clinical staging and other risk factors with PTB.

Methods: A cross-sectional study was conducted to estimate the PTB prevalence. Probable associated risk factors in PLWHAs with and without PTB were compared. The association between WHO clinical staging and other risk factors with PTB was investigated using bivariate analysis. A p -value < 0.05 was considered statistically significant.

Results: This study was conducted from January 2018 to December 2019, recruited about 584 participants with presumptive PTB and 20.72% (121) confirmed with PTB. In the bivariate analysis; participants who are on human immunodeficiency virus (HIV) Stage 4 (WHO clinical staging) were significantly more likely to develop PTB ($p=0.000$). PTB was significantly higher among male than female ($p=0.000$), higher among the older ($p=0.030$). PTB was significantly more frequent among participants with lower cluster differentiation 4 (CD4) cell counts ($p=0.042$). A contact history with a Tuberculosis (TB) patient was an important risk factor ($p=0.000$). PTB was significantly associated with smoking history ($p=0.000$).

Conclusion: A high PTB prevalence was observed. There was a significantly association between the severity of WHO clinical staging, sex, age, lower CD4 cell count, a contact history with a tuberculosis (TB) patient and smoking history with PTB among PLWHAs.

Keywords: PLWHAs, WHO clinical staging, Associated risk factors, PTB

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INTRODUCTION

World Health Organization (WHO) (2012) estimated 1.1 million new TB were found among people living with HIV/AIDS (PLWHA). TB is still as a leading cause of morbidity and mortality among PLWHAs, including those on highly active anti retroviral therapy (HAART) [1-3]. The co-infection of the human immunodeficiency virus (HIV) and PTB is one of a major public health problem worldwide [4, 5]. HIV infection is associated with an increased of TB rate and with changed of clinical manifestations, especially in the advanced stages. PTB occurs in about 75% of all PLWHAs with TB [4]. The increasing rate of HIV infection is associated with an impact on TB epidemiology [6, 7].

A comprehensive strategy focusing on risk factors of TB is essential [8]. There is not enough data of the prevalence and various PTB risk factors among PLWHAs in our Hospital. The probable risk factors of PTB such as WHO clinical stage, sex, age, educational status, marital status, occupation, route of transmission, adherence to HAART, CD4 cell count, TB contact of the family and smoking history. The aim of this study is to estimate the prevalence of PTB and to verify the risk factors associated with PTB among PLWHAs who visited for assessing HAART.

MATERIALS AND METHODS

Setting and study participants

This study was conducted in PLWHAs, visiting Merpati clinic at Wangaya hospital in Denpasar, Bali, Indonesia for their eligibility of assessing HAART.

Study design and data collection

We conducted a cross-sectional study to estimate the prevalence of PTB and analysed the data comparing PLWHAs with PTB and

without PTB, to verify the associated risk factors of PTB. The study team explained to participants; confidentiality assured, the anonymity of the collected data. An informed consent was obtained from all the participants. Information about age, sex, educational status, a history of TB contact, CD4 cell count, WHO clinical staging of HIV infection and others data was collected from participant medical records.

Definition of study variables

World Health Organization (WHO) PTB diagnostic criteria includes a clinical symptoms/TB screening and a Chest X-Ray suggestive of TB, mycobacterium tuberculosis (MTB) culture or Acid Fast Bacilli/AFB (sputum smear microscopy) when culture is unavailable [9].

In this study, the participants were adult PLWHAs who were confirmed PTB (positive clinical symptoms/TB screening, suggestive of TB on Chest X-ray and positive for Acid Fast Bacilli/AFB by direct microscopy or PLWHAs who had a prior data of medical record of being confirmed with PTB referral from other health-care facilities.

The case definitions and clinical staging of HIV/AIDS regarding to WHO are clinical stage 1 (asymptomatic) and stage 2-4 with a symptoms (acquired immune deficiency syndroms/AIDS) [10].

Statistical analysis

Descriptive test was performed to describe the participant characteristic data. Data were analyzed using SPSS version 18 and the data compared the participants with PTB and without PTB. Chi-square test was used to evaluate the association between risk factors with the prevalence of PTB. The significance of the variable associations are obtained in the bivariate analysis ($p < 0.05$).

Ethics

Ethical clearance was obtained No: 08/RSUDW/litbang/2018 from the local ethical committees. We collected data from the participants who visited Wangaya Hospital and completed at least two years follow-up from the ethical clearance granted to date.

RESULTS

A total of 584 PLWHAs were included in the study from January 2018 to December 2019. We found 121 (20.72%) among 584 people living with HIV/AIDS were confirmed with Pulmonary Tuberculosis, are shown in fig. 1.

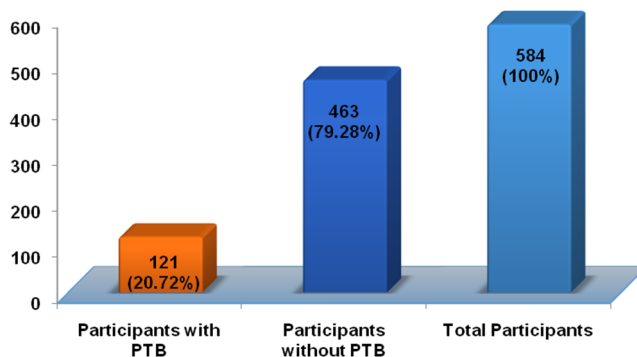


Fig. 1: The comparative data of participants

Among PLWHAs with PTB, 71.9% were male, 61.2% were with the age ≥ 34 y old, 83.5% were HIV stage 3, the median of CD4 cell count

(251 cells/ μ l) and 69.4% were with smoking history, are shown in table 1.

Table 1: Clinical and socio-demography characteristic of participants/PLWHAs with PTB (N=121)

Variables	Total N (%)
WHO clinical staging	
- 1	0
- 2	0
- 3	101 (83.5)
- 4	20 (16.5)
Sex	
- Male	87 (71.9)
- Female	34 (28.1)
Age: median of age: 34 y	34
- <34	47 (38.8)
- ≥ 34	74 (61.2)
Educational status	
- Elementary school	10 (8.3)
- Junior high school	28 (23.1)
- Senior high school	66 (54.5)
- University	17 (14.0)
Marital status	
- Unmarried	28 (23.1)
- Married	77 (63.6)
- Divorced/widowed	16 (13.2)
Occupation	
- Yes	107 (88.4)
- No	14 (11.6)
Route of transmission	
- IV drug user	2 (1.7)
- Non-IV drug user	119 (98.3)
Adherence to HAART	
- Good	117 (96.7)
- Poor	4 (3.3)
CD4 cell count median (cells/ μ l)	251
CD4 cell count (cells/ μ l)	
- <305	56 (58.9)
- ≥ 305	39 (41.1)
Contact history with PTB patient	
- Yes	27 (22.3)
- No	94 (77.7)
Smoking history	
- Yes	84 (69.4)
- No	37 (30.6)

In bivariate analysis, the risk factors that significantly associated with PTB are male ($p=0.000$), PLWHAs with PTB are more likely to be older ($p=0.030$), more advance in WHO clinical staging ($p=0.000$), lower CD4 cell count ($p=0.042$), are prior with TB contact ($p=0.000$) and the majority with smoking history ($p=0.000$). All are shown in table 2.

Table 2: Bivariate analysis of participants/PLWHAs (N=584)

Variables	Pulmonary tuberculosis (PTB)		Total (N)	p-value
	Yes; N (%)	No; N (%)		
WHO clinical staging				0.000*
- 1	0 (0.0)	63 (100.0)	63	
- 2	0 (0.0)	54 (100.0)	54	
- 3	101 (25.6)	293 (74.4)	394	
- 4	20 (27.4)	53 (72.6)	73	
Sex				0.000*
- Male	87 (26.1)	246 (73.9)	333	
- Female	34 (13.5)	217 (86.5)	251	
Median age of HIV diagnosis (year)	37	33	34	
Age of HIV diagnosis (year)				0.030*
- <34	47 (16.9)	231 (83.1)	278	
- ≥34	74 (24.2)	232 (75.8)	306	
Educational status				0.278
- Elementary school	10 (20.4)	39 (79.6)	49	
- Junior high school	28 (27.5)	74 (72.5)	102	
- Senior high school	66 (18.6)	289 (81.4)	355	
- University	17 (21.8)	61 (78.2)	78	
Marital status				0.333
- Unmarried	28 (24.6)	86 (75.4)	114	
- Married	77 (19.1)	327 (80.9)	404	
- Divorced/widowed	16 (24.2)	50 (75.8)	66	
Occupation				0.650
- Yes	107 (20.5)	416 (79.5)	523	
- No	14 (23.0)	47 (77.0)	61	
Route of transmission				0.111
- IV drug user	2 (66.7)	1 (33.3)	3	
- Non-IV drug user	119 (20.5)	462 (79.5)	581	
Adherence to HAART				0.565
- Good	117 (20.6)	452 (79.4)	569	
- Poor	4 (26.7)	11 (73.3)	15	
CD4 cell count median (251 cells/μl)				
CD4 cell count (cells/μl)				0.042*
- <251	56 (26.8)	153 (73.2)	209	
- ≥251	39 (18.5)	172 (81.5)	211	
Contact history with a TB patient				0.000*
- Yes	27 (75.0)	9 (25.0)	36	
- No	94 (17.2)	454 (82.8)	548	
Smoking history				0.000*
- Yes	84 (96.6)	3 (3.4)	87	
- No	37 (7.4)	460 (92.6)	497	

*bivariate analysis (p<0.05).

DISCUSSION

A cross-sectional study was carried out from January 2018 to December 2019, recruited PLWHAs with and/or without PTB.

HIV co-infection was the most potent immunodeficiency risk factor for developing Pulmonary tuberculosis [11].

This study found that among 584 total participants, 20.72% (121 PLWHAs) were confirmed with PTB. The prior studies were reported wide range of the PTB prevalence among PLWHAs. Mama *et al.* (2018) reported, of the 291 PLWHAs screened, the overall PTB prevalence rate of 7.2% [12]. Negussie *et al.* (2018), found 36.9% of the study participants were confirmed PTB [13]; and Tiwari *et al.* (2019), reported a high prevalence of PTB was observed 32.4% PTB [14].

We explored a WHO clinical staging and other risk factors by interviewing with a semistructured questionnaire and completed by data from the participant medical records.

In this study, PLWHAs with Stage 4 (WHO clinical staging) were more likely to develop PTB (p=0.000). Similar evidences were reported by Taha *et al.* (2011), that PLWHAs who with Stage 4 (WHO clinical staging) were more likely to develop PTB compared with Stage 3 (WHO clinical staging) (69.1% vs 30.9%; p<0.001) [8]. Kibret *et al.* (2013), found PTB patients were more likely to have baseline Stage 3 (WHO clinical staging) or Stage 4 (COR=4.51; 95% CI: 3.032, 6.70) [15]. Belay *et al.* (2013), revealed that more than

two-third of TB cases were in Stage 3 (WHO clinical staging) [16]. Roselinda *et al.* (2015), PLWHAs with Stage 4 (WHO clinical staging) were more at risk for developing PTB [17]. Awadalla *et al.* (2015), reported that PLWHAs with Late clinical WHO stages to be risk factors for developing PTB (AOR: 5.86; 95% CI: 1.88-17.96; p<0.01) [18]. Tesfaye *et al.* (2018), found a significant association between advanced WHO stage and TB-HIV/AIDS co-infection (OR: 6.81; 95% CI: 3.91-11.88) [19].

We found a significantly association between the risk of developing PTB among PLWHAs with sex (male) was more likely (p=0.000). Carvalho (2008), also found that male was a high-risk factor for developing PTB [20]. It is unclear whether the more frequent in males due to the differences in social behavior. From a study conducted in South-western Uganda by Boum *et al.* (2014), they concluded TB prevalence was higher among male than female people with presumptive TB and it was independent of other TB risk factors [21]. Horton *et al.* (2016) concluded that TB prevalence was higher in men due to a disadvantage in seeking or accessing TB care in many settings [22]. One study by Dovonou (2017) in West Africa also showed that male gender was a potential risk factor of TB treatment failure [23].

The older age was more likely to develop PTB; this study found that the older participants were more frequent to develop PTB (p=0.030). It is in accordance with a study by Keizer *et al.* Their prospective study showed age above 33 y increased the risk for tuberculosis

substantially [24]. Tiwari *et al.* (2019) reported PLWHAs with PTB were more likely to be older. A cross-sectional study in Iran also showed that adults and elderly comprised the highest proportion of TB [14]. Ghaffari-Fam (2015), their study showed that adults and elderly comprised the highest proportion of TB [25].

Our study found that PLWHAs had a very poor immune status. The median CD4 cell count was 251 cells/ μ l and was significantly associated with PTB ($p=0.042$). Similar with other study, Chang *et al.* (2015) found that lower CD4 count was a high-risk factor for developing PTB ($p<0.01$) [26], and Tiwari *et al.* (2012) reported that lower CD4 count was significantly associated with risk for developing PTB ($p<0.001$) [14]. The connection between risk of tuberculosis in HIV and low CD4 count was mentioned in a lot of study and most of them showed that a low CD4 count had a strong risk factor for the incidence PTB [27, 28]. From a systemic review and meta-analysis by Ellis *et al.* (2017), an estimated a 1.43 fold increase (95%CI: 1.16-1.77) in TB incidence per 100 cells/ μ l decreased in CD4 cell count [29]. We revealed in this study, of total 71.08% of tuberculosis infection occurred in low CD4 level (<80 cells/ μ l) and from an analysis that CD4 below 80 cells/ μ l had a significant association with a higher risk of tuberculosis infection (OR=6.043 95%CI: 3.089-11.823) compared to CD4 count greater than 80 cells/ μ l. Belay *et al.* (2013) in their study conducted in Ethiopia stated that individual HIV cases whose CD4 count less than 200 cells/ μ l were more than seven times likely to develop tuberculosis compared to CD4 count more than 500 cells/ μ l [16].

A retrospective study by Chang *et al.* (2015) in Nigeria also found that CD4 cell counts were significant predictors of TB, with CD4 cell counts >350 cells/ μ l had one third the risk of developing TB compared with those with CD4 cell counts ≤ 100 cells/ μ l [26]. Sutariya *et al.* (2015), documented that lower CD4 count was strongly associated with the higher odds of PTB [27]. Sudre *et al.* (1996) reported that participant with CD4 <50 cells/ mm^3 were eight times more likely (AOR 7.8; 95% CI 7.3-8.3) and those with 50-200 CD4 cells/ mm^3 more than four times more likely (AOR 4.9; 95% CI 4.4-5.4) to have tuberculosis than patients with CD4 >500 cells/ mm^3 [28].

This study found that a history of contact with a TB patient was significantly associated with PTB ($p=0.000$). Taha *et al.* (2011), reported that the presence of TB patients in the family was significantly associated with PTB ($p<0.001$) [8]. Swarna (2014), in Malaysia found 30% of participants of pulmonary tuberculosis contact had positive tuberculin skin test (TST) compared to 53% of the participants without HIV infection [OR=0.41, 95% CI 0.07-0.87; $p=0.016$] [30].

Smoking history, this study found that smoking history was significantly associated with PTB ($p=0.000$). Other study by Kibret *et al.* (2013), also found that smoking history was more likely associated with PTB ($p<0.0001$) [15]. Similarly, with Swarna (2014), reported that in Malaysia, the cigarette prevalence rate was high among participants with TB. Forty percent to fifty percent of TB participants were smokers and smoking prevalence was 57% of PTB [30]. Gjergji *et al.* (2018) reported that coinfection TB-HIV was more prevalent in smokers [31].

CONCLUSION

Most of PLWHAs having a poor clinical condition and the state of the immunity are reported to be predisposition factor of PTB. A high PTB prevalence among PLWHAs is observed. All PLWHAs should be screened for TB. In the presence of the risk factors, intensified screening is highly recommended. There is a significant association between the clinical severity of PLWHAs (WHO clinical staging), sex, age, lower CD4 cell count, a contact history with a TB patient and smoking history with PTB.

LIMITATIONS

This study is a hospital-based; thus the findings might not be generalizable. PTB diagnostic uses only smear microscopy of AFB staining. Microscopy is a less sensitive method compared with culture. The cultural technique is not performed because of the limited laboratory facilities.

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AUTHORS CONTRIBUTIONS

Ketut Suryana made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. Hamong Suharsono took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. Noviana Joenputri revised it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work

CONFLICT OF INTERESTS

No conflict of interest among the authors.

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