

**BUKTI KORESPONDENSI ARTIKEL PADA JURNAL
INTERNASIONAL BEREPUTASI**

PENGUSUL:

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UNIVERSITAS NEGERI SEMARANG

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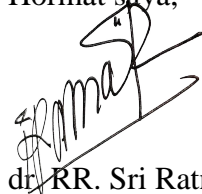
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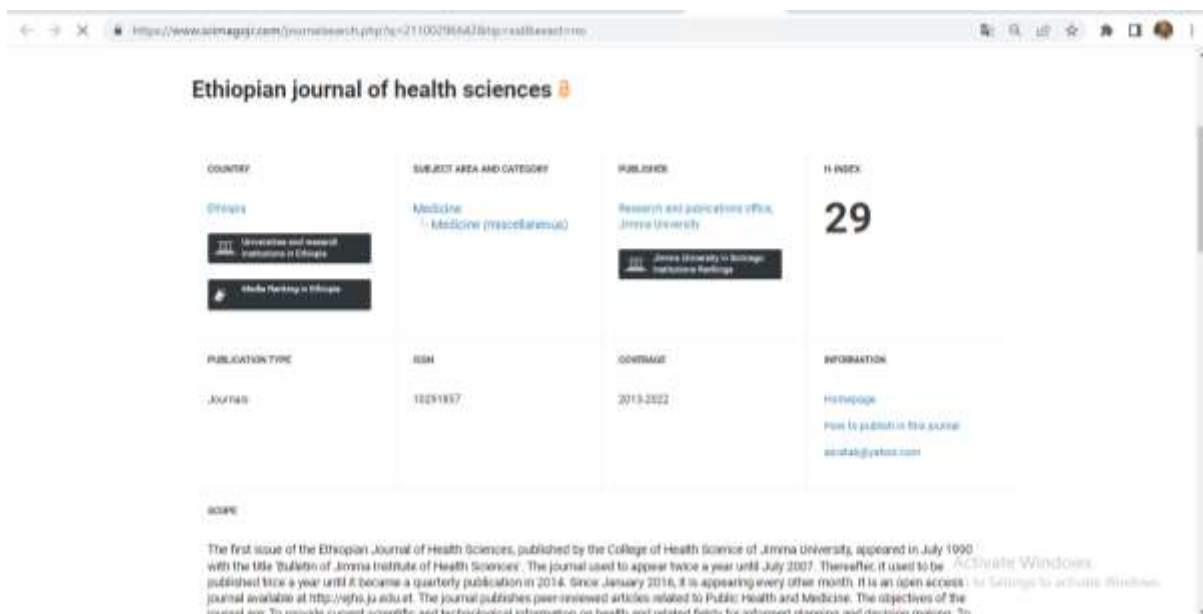


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KRONOLOGI KORESPONDENSI PUBLIKASI ARTIKEL PADA JURNAL INTERNASIONAL BEREPUTASI DAN BERFAKTOR DAMPAK

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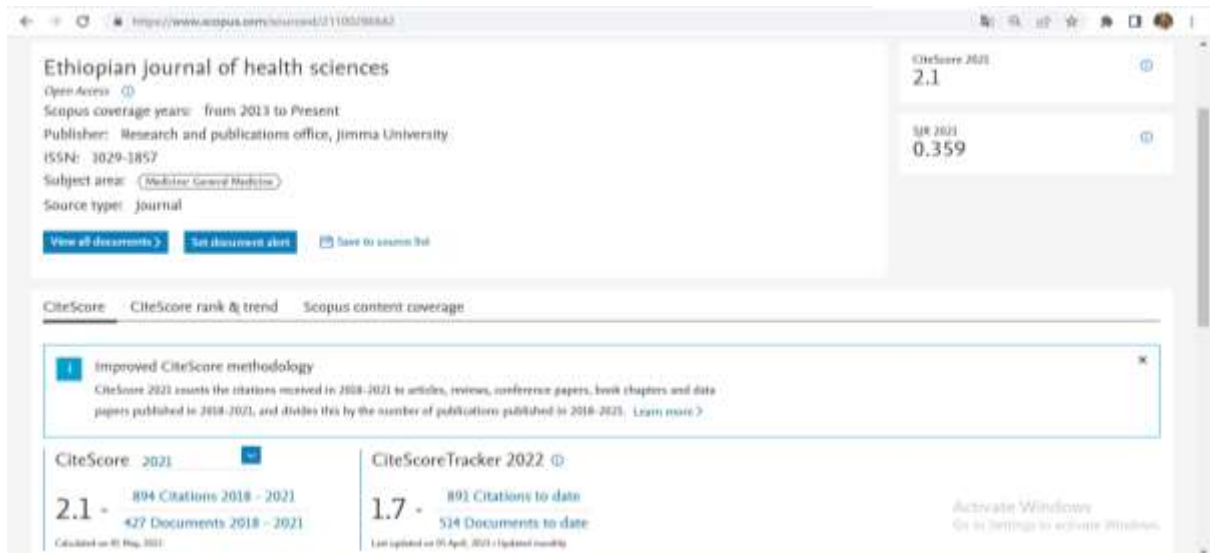
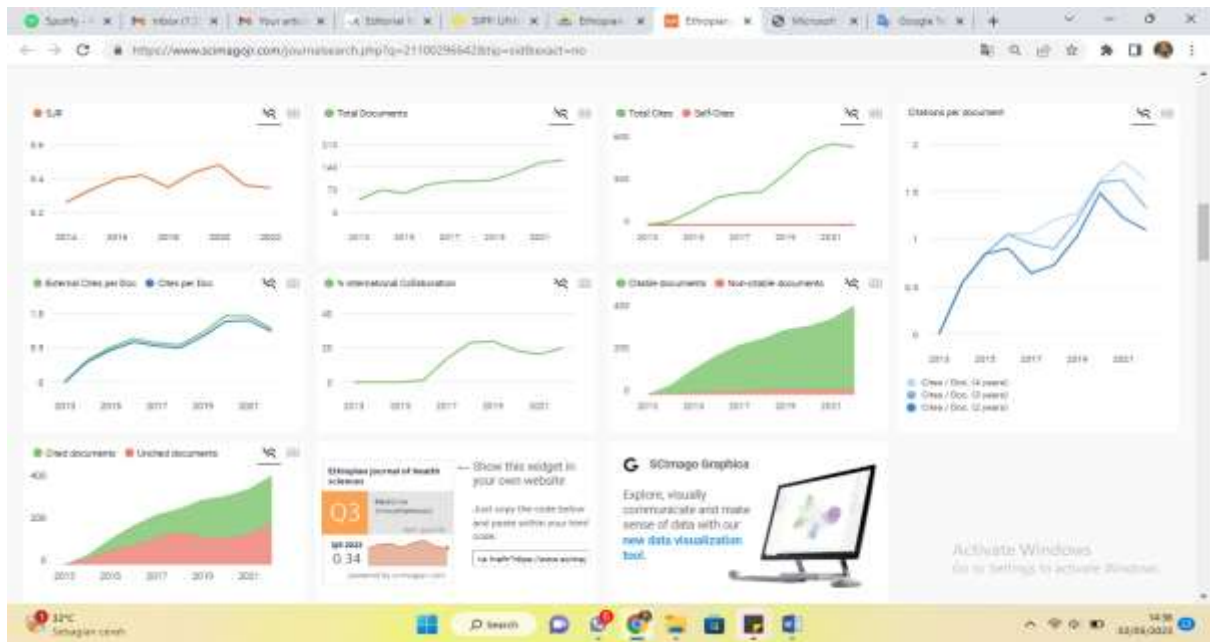


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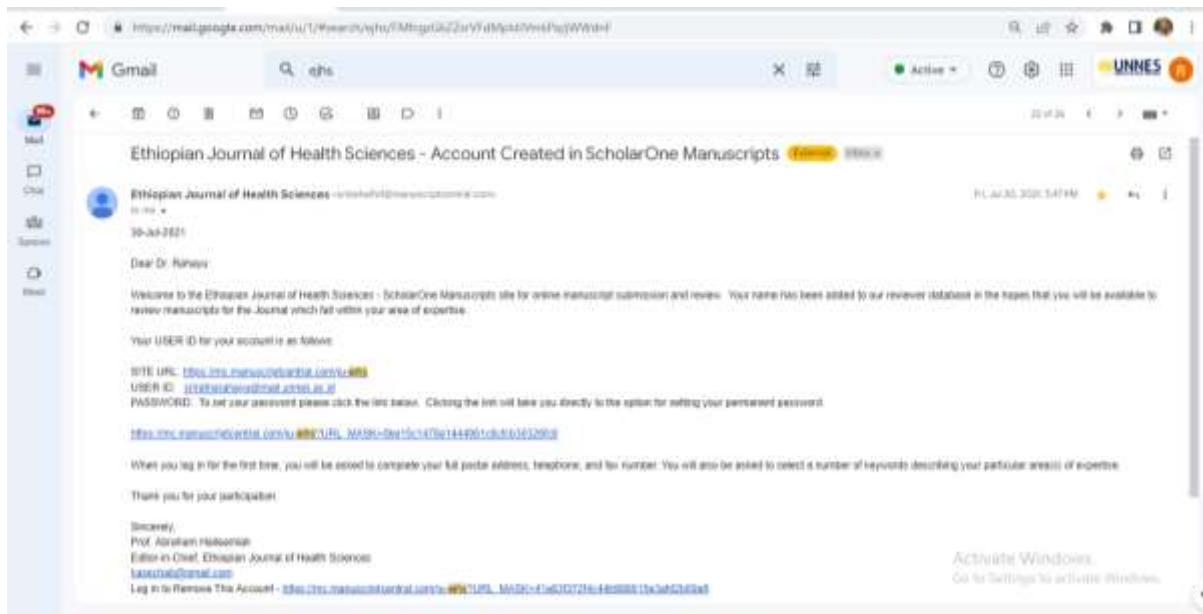
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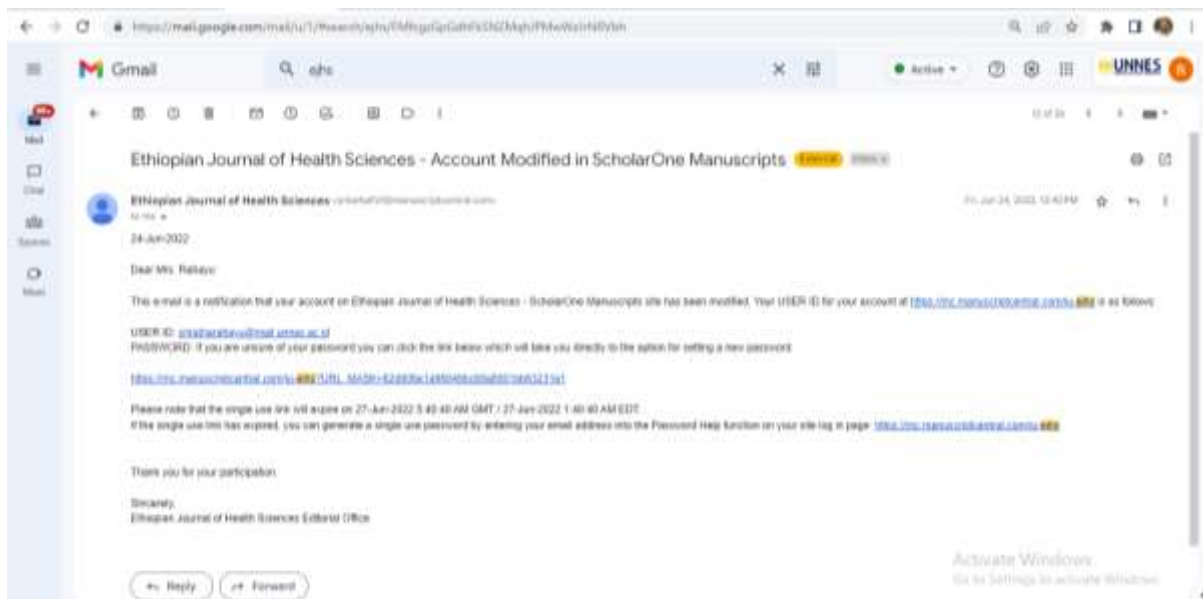
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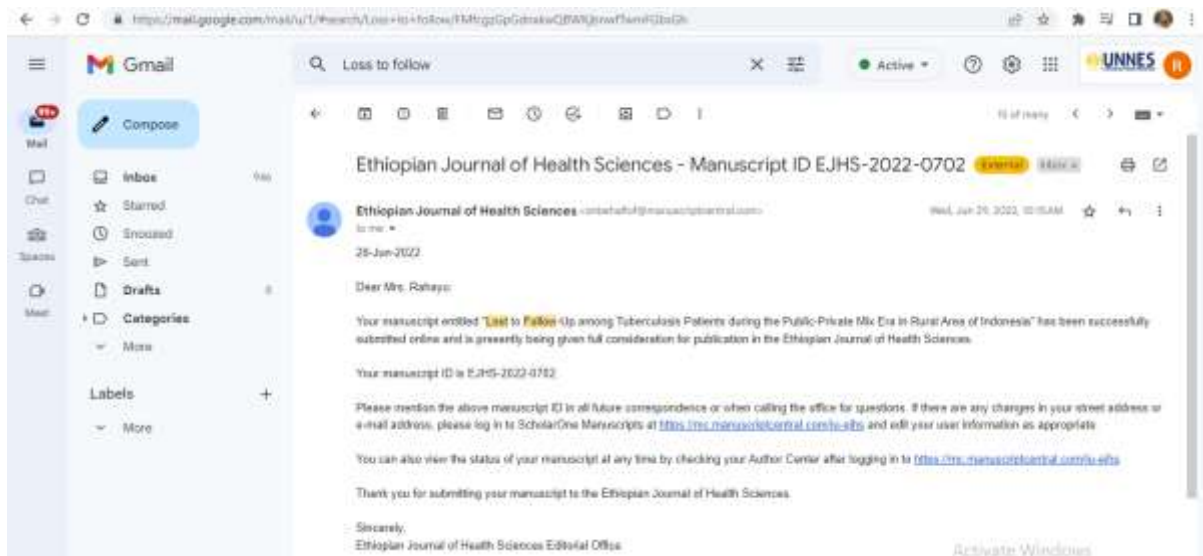
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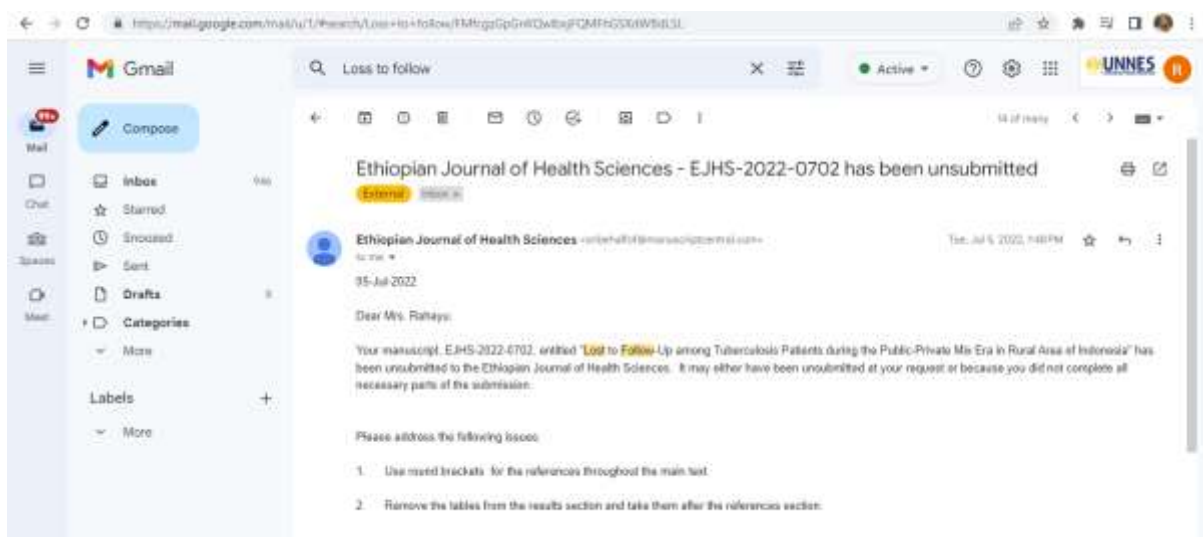
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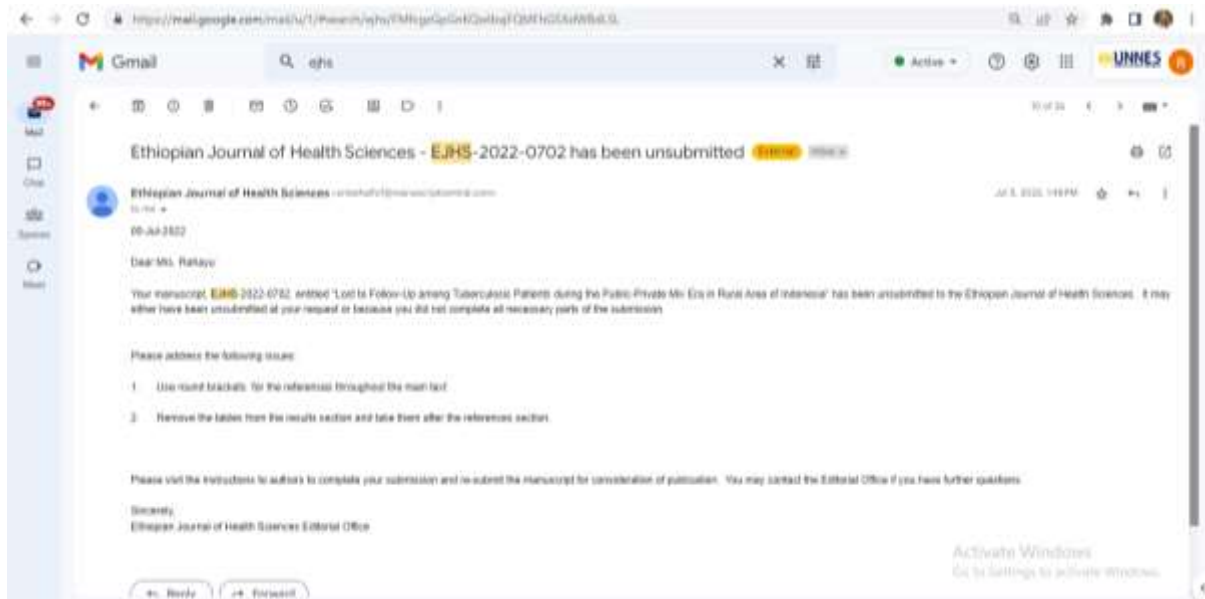
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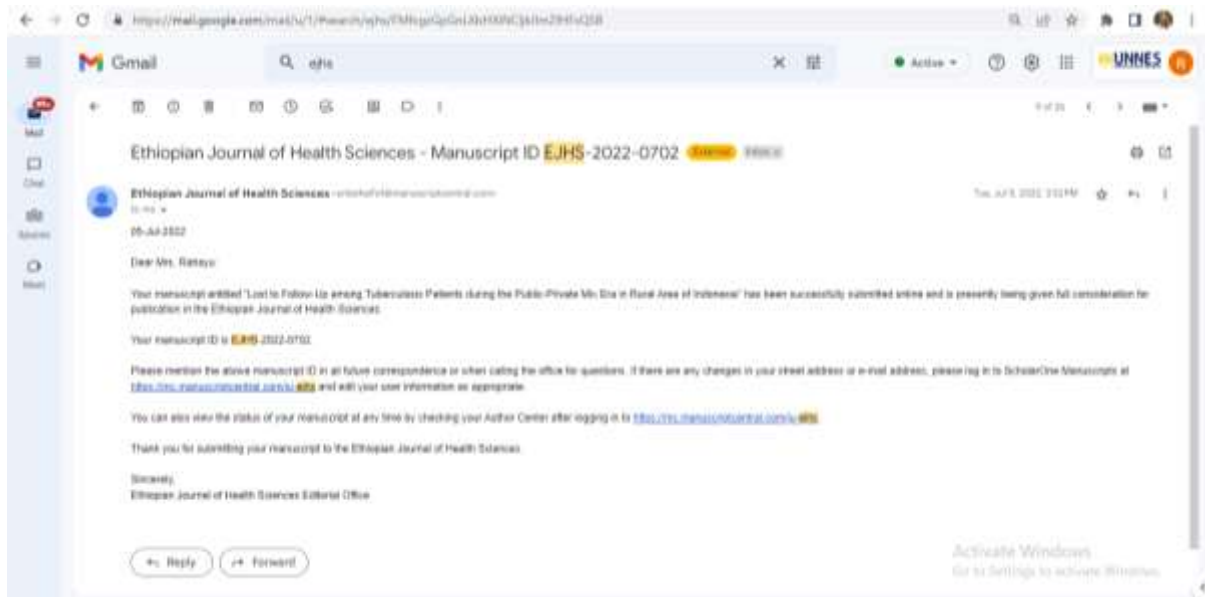
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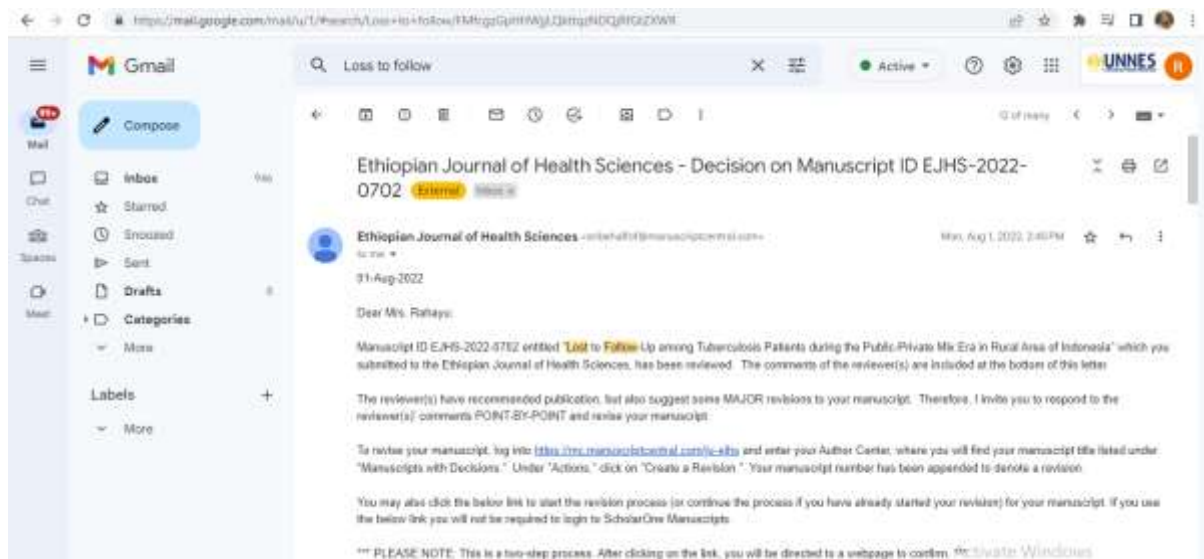
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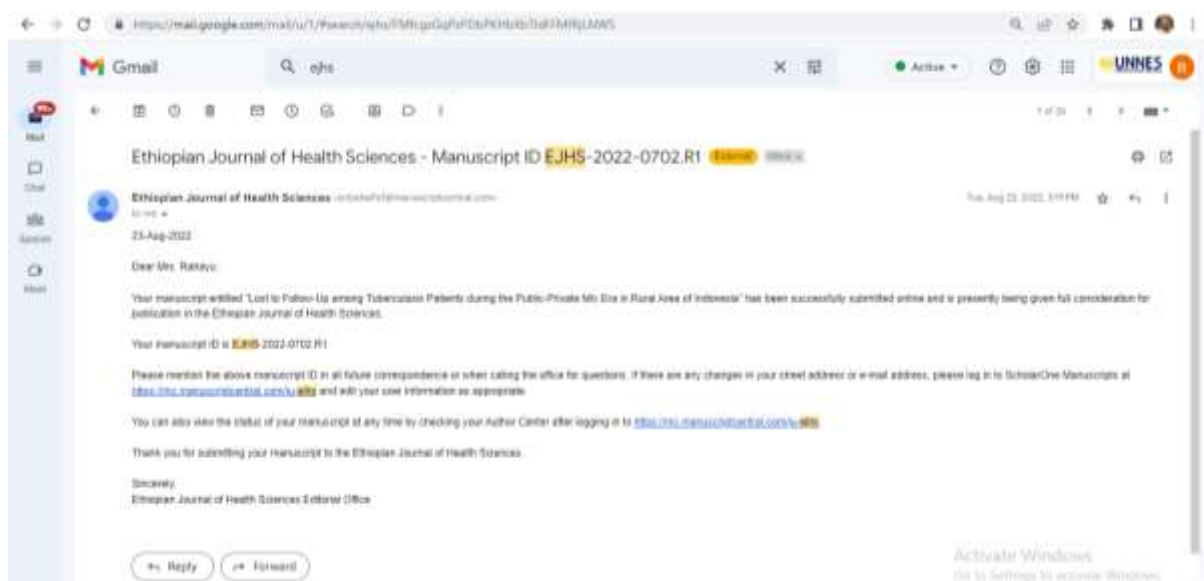
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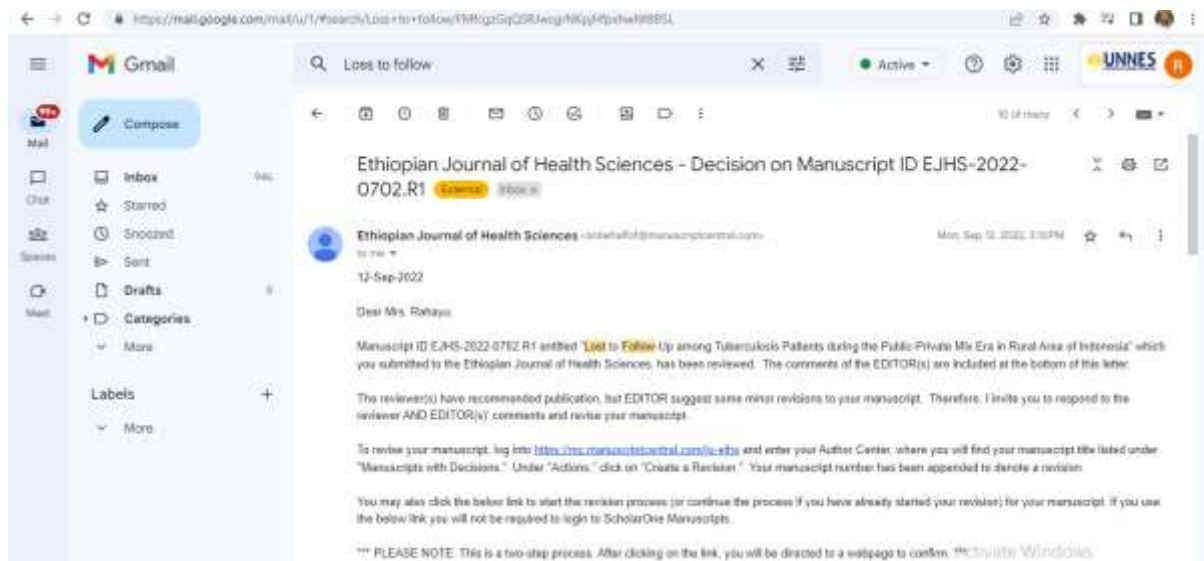
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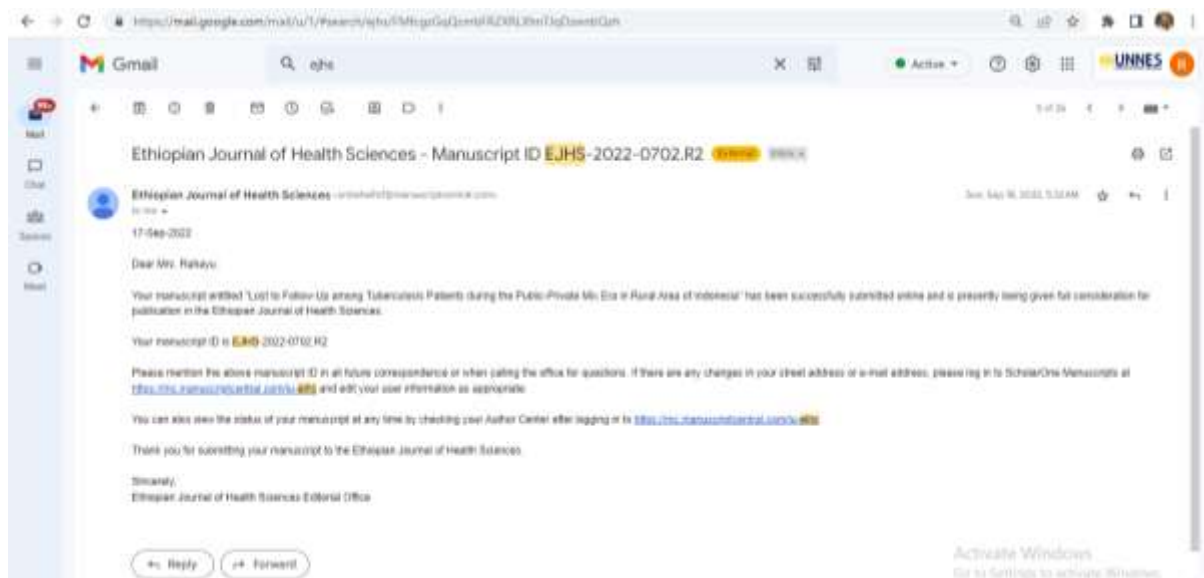
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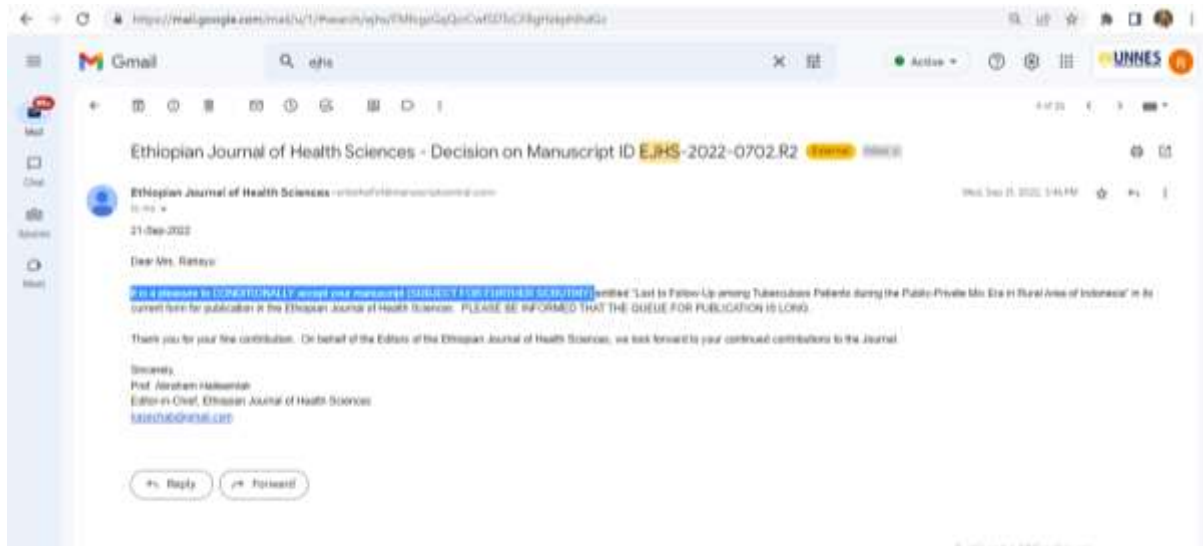
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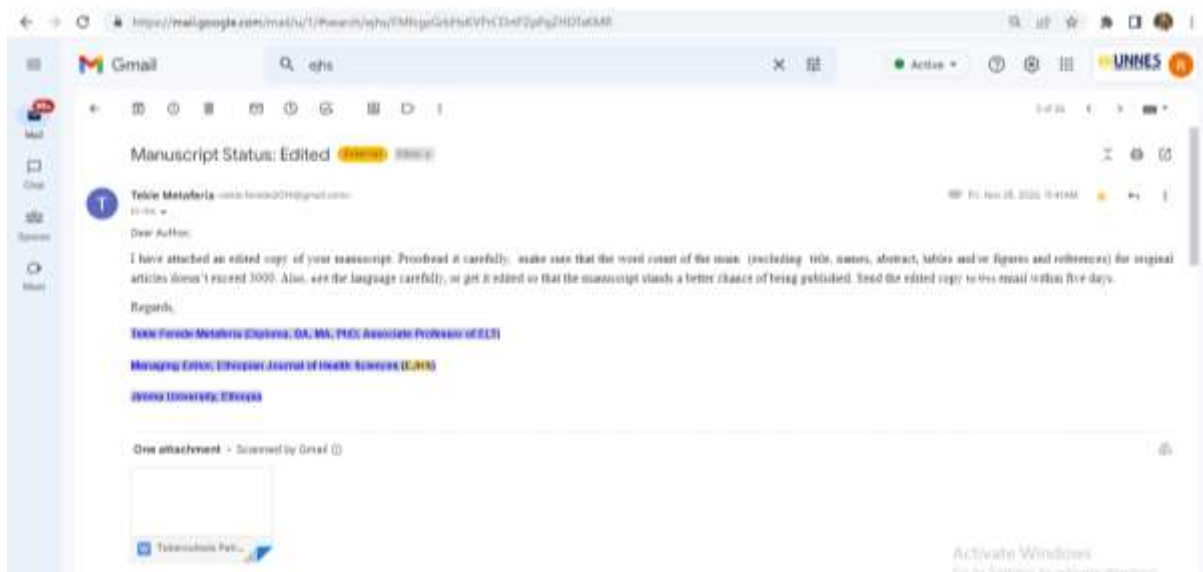
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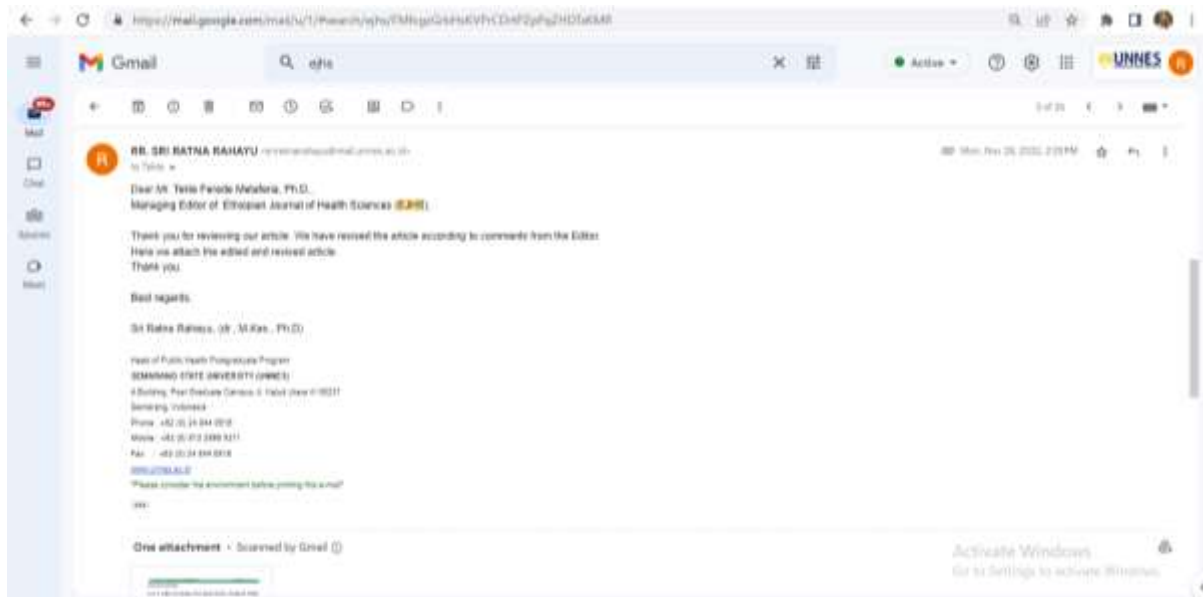
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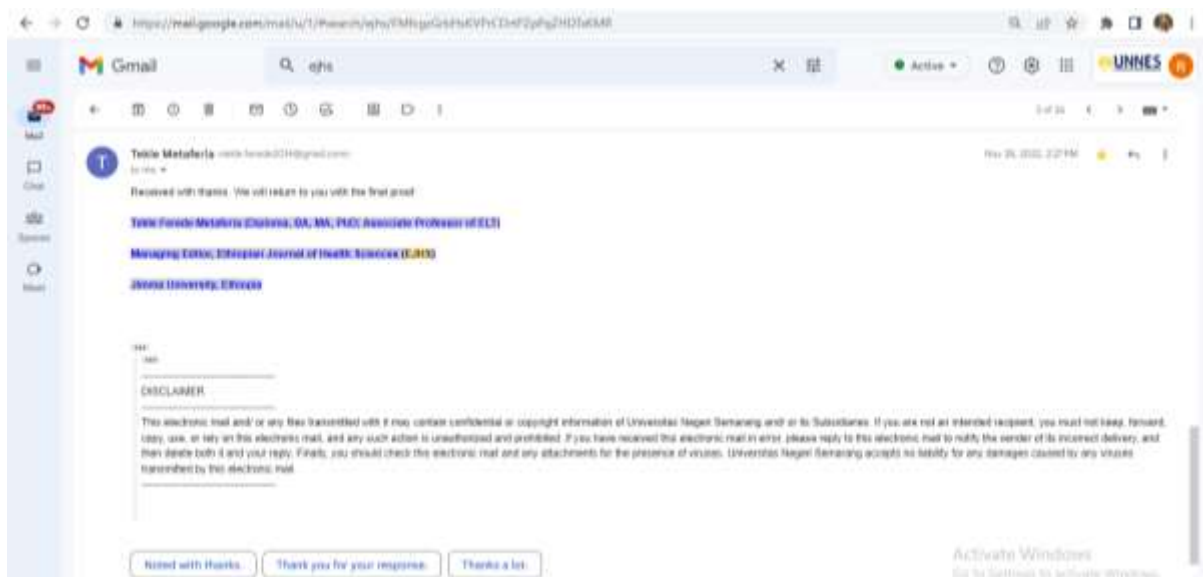
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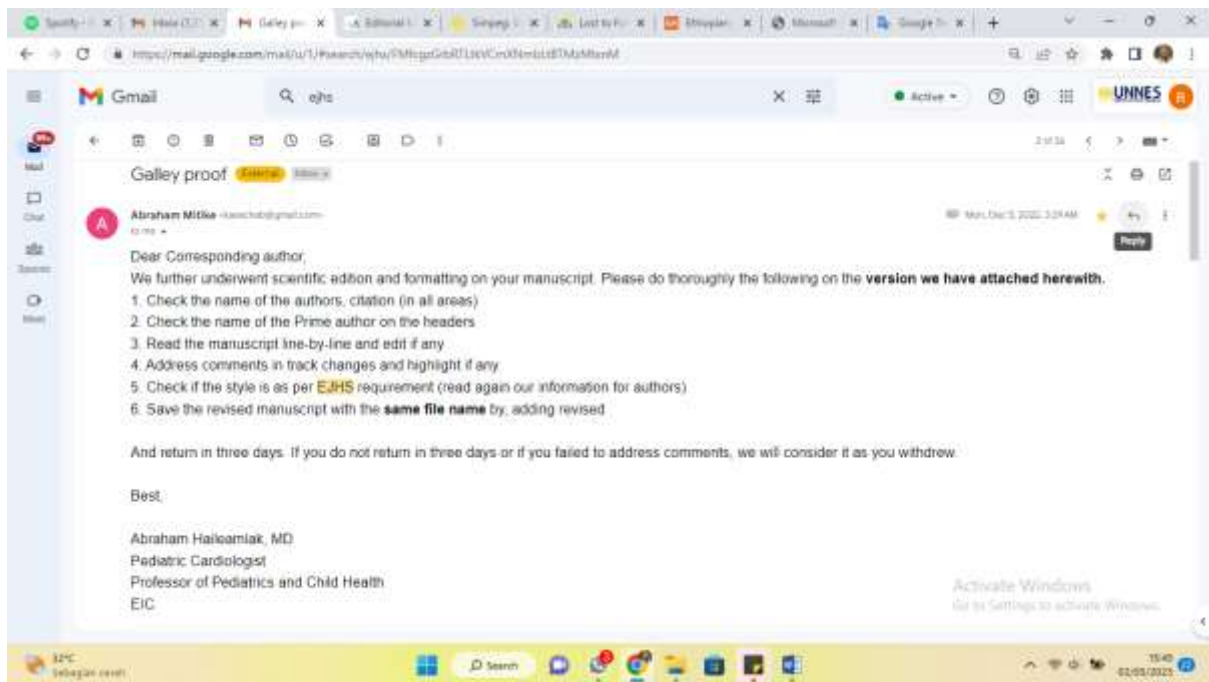
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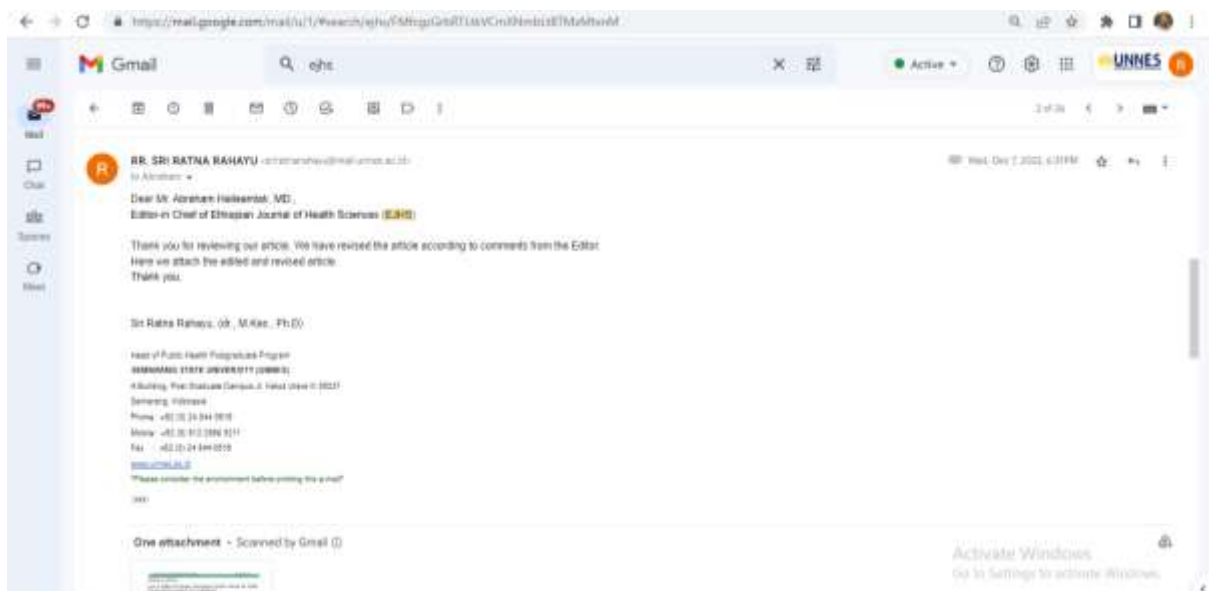
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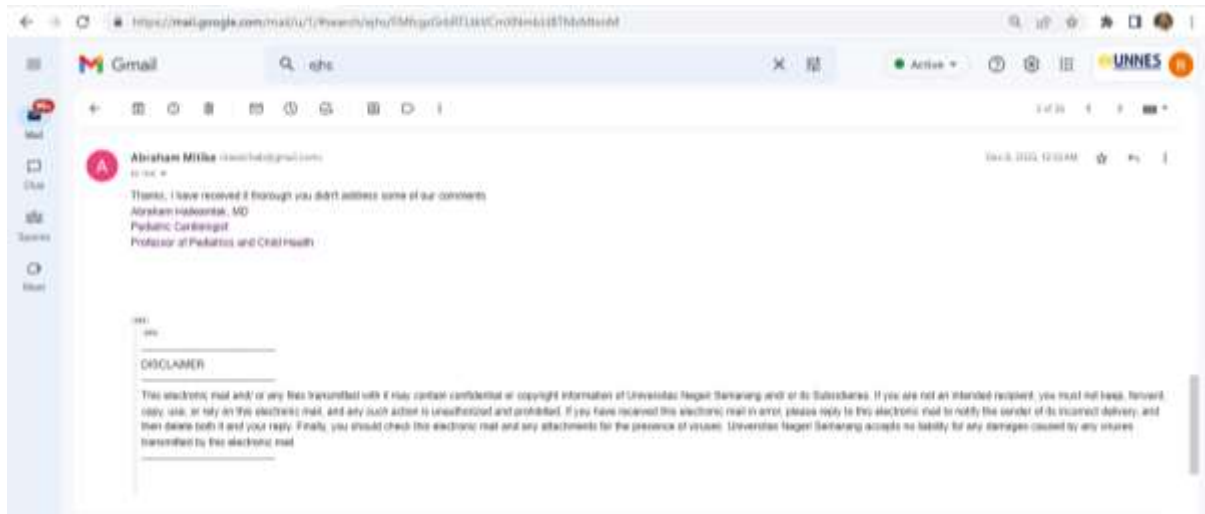
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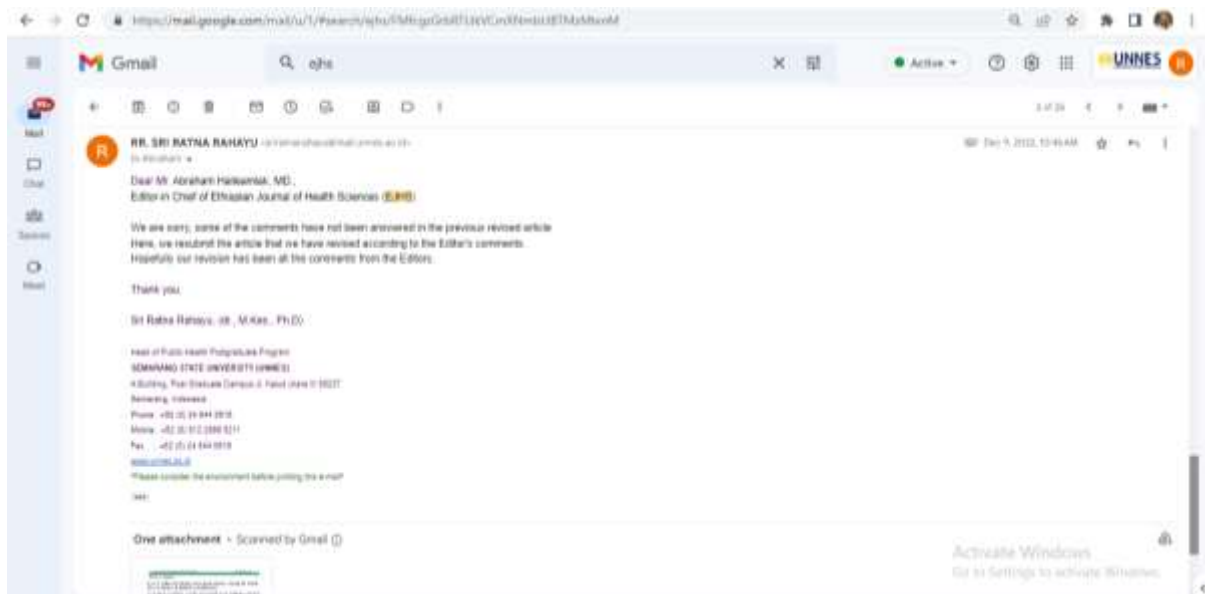
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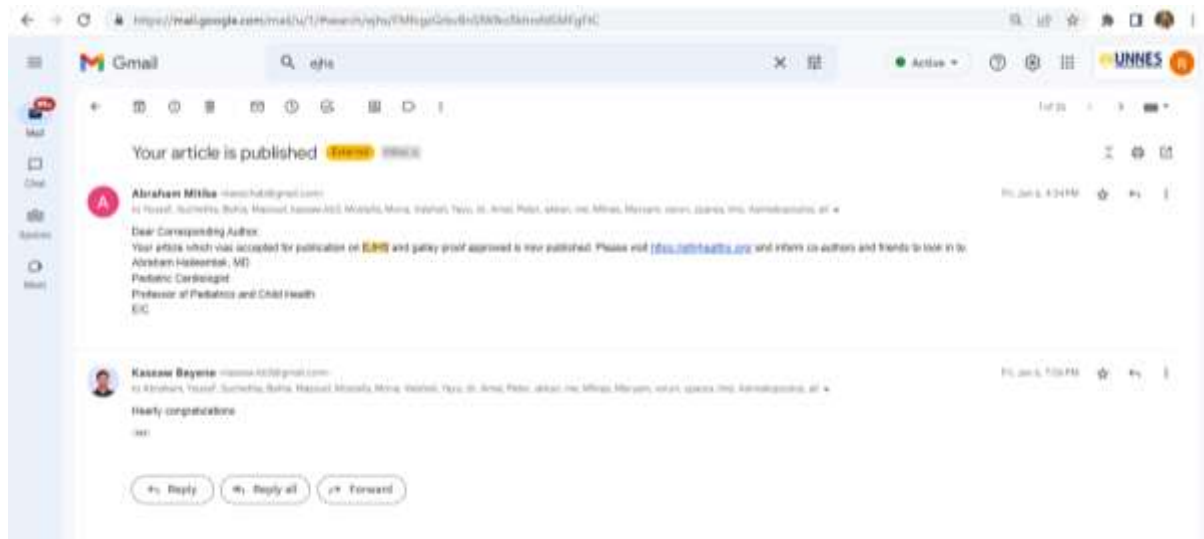
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Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia

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Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia

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Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia

Abstract

Background: Indonesia's national Tuberculosis (TB) strategy is public-private mix (PPM). The PPM aims to treat patients who have lost sight during TB treatment as these patients are TB carriers and at risk of transmitting TB. The purpose of this study was to identify predictive factors for loss to follow-up (LFTU) among TB patients receiving treatment when the PPM was at place in Indonesia.

Methods: The design of this study was a retrospective cohort study. The data used in this study was sourced from the Tuberculosis Information System (SITB) of Semarang which was recorded routinely during 2020-2021. Univariate analysis, crosstabulation, and logistic regression were performed on 3434 TB patients meeting the minimum variables.

Results: The participation of health facilities in reporting TB during the PPM era in Semarang reached 97.6% consisting of 37 primary healthcare center (100%), 8 public hospitals (100%), 19 private hospitals (90.5%), and a community-based pulmonary health center (100%). The regression analysis reveal that the predictive factors of LTFU-TB during the PPM are the year of diagnosis (AOR=1.541; p-value=<0.001; 95% CI=1.228-1.934), referral status (AOR=1.562, p-value=0.007; 95% CI=1.130-2160), healthcare and social security insurance ownership (AOR=1.638; p-value=<0.001; 95% CI=1.263-2.124), drugs source (AOR=4.667; p-value=0.035; 95% CI=1.117-19.489).

Conclusions: The PPM strategy in dealing with LTFU patients should focus on TB patients without Healthcare and Social Security Insurance and who receive TB treatment rather than program drugs.

Keywords: Health Facilities, Lost to Follow-Up, Tuberculosis, Indonesia

Introduction

Tuberculosis (TB) is an infectious disease that remains a major health problem worldwide. In 2019, the number of people diagnosed and confirmed TB cases reached 7.1 million globally[1]. World Health Organization (WHO) estimates that there is a 2.9-million gap between the number of diagnosed TB cases and the number of notified cases due to the high unreported cases. One country that accounts for more than half of the global gap is Indonesia (10%)[2]. Indonesia's national TB strategy is public-private mix (PPM) which primarily aims to increase TB case detection[3,4]. The case network is one of the PPM network's principles, namely the continuity of treatment of TB patients from referrals/transfers and the tracking of TB patients who are lost to follow-up[5].

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3 The PPM approach is to ensure equitable, quality, and sustainable access to TB services
4 for those affected by TB (universal access) in ensuring TB patients' recovery. However, within
5 the Indonesian context, private sector involvement remains low[4]. According to Indonesia
6 National Development Planning Agency, the private sector manages more than 50% of
7 hospitals, provides 60% of outpatient care, and 43% of hospitals with inpatients[4,6]. The
8 Patient Pathway Analysis (PPA) study in 2017 revealed that 54% of the discovery and treatment
9 of TB has been carried out by government health facilities, and 42% by the private sector.
10 Private health facilities such as private clinics contribute only 1%, while private hospitals
11 contribute 8%[7]. However, only 32% of cases are recorded, indicating that 68% of cases go
12 unreported. Most of these missing cases are believed to be in the private sector and go
13 unreported, even though some of them can receive both diagnosis and treatment at the same
14 time.

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The success of tuberculosis control in Indonesia can be described by three indicators. They are complete treatment rate (% complete rate), cure rate (% cure rate), and treatment success rate (% success rate). TB patients are therefore classified as cured, completed treatment, failed treatment, lost to follow-up, or died based on the outcome of their treatment. Lost to follow-up (LTFU) was defined as patients who received treatment for at least 4 weeks and the treatment was discontinued for more than eight consecutive weeks[8].

One of the reasons for the development of acquired Drug Resistance Tuberculosis (DR-TB) is LTFU. Patients who are readmitted after LTFU are more likely to redevelop infectious active TB and are at higher risk of developing further drug resistant strains of tuberculosis[9,10]. According to reports on the economic challenges of TB drug non-adherence, an estimated 52 MDR-TB patients lost to follow-up resulted in 5 patients developing XDR-TB, 3 newly infected MDR-TB and a new XDR-TB, and 3 deaths[11].

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3 LTFU can increase the risk of clinical deterioration, treatment failure, and further
4 complications in tuberculosis patients. Patients who discontinue treatment too early are one of
5 the leading causes of treatment failure[11]. The dropout rate is critical because low LTFU as a
6 result of improved TB management will reduce re-treatment case by 10-20% in the coming
7 years[5]. This issue highlights the importance to study the predictors of LTFU during the PPM.
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17 **Methods**

18 *Study design and data source*

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20 The design of this study was a retrospective cohort study. This study integrates data from the
21 Tuberculosis Information System (SITB) via the TB03 form provided by the Ministry of
22 Health. This system summarizes tuberculosis patient data and treatment monitoring. The
23 research data is collected from 2020 to mid-2021.
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33 *Data Management and Analysis*

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35 **Dependent variable:** Patients whose tuberculosis treatment status was lost to follow-up were
36 defined as discontinuing treatment for two or more consecutive months (8 weeks) for any reason
37 without medical consent[11].
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42 **Independent variables:** The independent variables that are fully recorded in the SITB and can
43 be included in the final analysis are the year of diagnosis, which is classified as 2020 or 2021
44 (January - July), healthcare and social security insurance ownership; standard of treatment;
45 gender; employment status; place of residence, which is classified as within the city of
46 Semarang or outside the city of Semarang; close contact examination, which we classify as
47 close contact examination is carried out or not carried out; and referral status which is classified
48 as referral patients or patients who come to health services on their own for TB tests; diagnostic
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3 methods; types of TB; patient status; Diabetes Mellitus status; HIV Status; and drugs source,
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5 which is classified as program drugs or drugs obtained outside of the program.
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7 ***Statistical Analysis***

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10 Based on variable categories, data is presented in terms of frequency and percentage. For the
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12 derivation cohort, bivariate analysis was used to identify risk factors associated with loss to
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14 follow-up, comparing subjects who recovered plus subjects who completed treatment with
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16 subjects who were lost to follow-up. To determine predictors of loss to follow-up, multivariable
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18 analysis was performed using logistic regression test. The patients with the lowest loss to
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20 follow-up were designated as the reference group. *P*-values of 0.05 or less were considered
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22 statistically significant.
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25 ***Ethical approval***

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28 The Health Research Ethics Committee of Universitas Negeri Semarang has reviewed and
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30 approved the protocol by issuing a letter numbered 095/KEPK/EC/2021.
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36 **Results**

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38 Health facilities in Semarang City consist of primary healthcare center, public and private
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40 hospitals, community pulmonary health center, as well as independent practice doctors and
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42 clinics which are reported through primary healthcare center and hospitals as referral health
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44 facilities. All 37 primary healthcare center in Semarang (100%) participated in reporting and
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46 recording TB cases. Likewise, 8 public hospitals and a primary healthcare center, all of them
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48 (100%) participated in the reporting and recording TB cases. However, out of 21 private
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50 hospitals in Semarang, only 90.5% private hospitals participated in reporting and recording TB
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52 cases. Detailed data are presented in Table 1.
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Table 1. Characteristics of health facilities at the research site

Type of Health Facilities	Number of health facilities reporting TB	Total of health facilities	%
Primary Healthcare Center	37	37	100
Public Hospitals	8	8	100
Private Hospitals	19	21	90.5
Community Pulmonary Health Center	1	1	100
Average			97.6

Characteristics of respondents based on Tuberculosis Information System (SITB) data are presented in Table 2. The average age of TB patients is 34.2 years old (SD: 28.9), with male patients (53.9%) outnumbering female patients. Most of them live in Semarang (77.4%), while the rest live in other neighboring cities. As many as 81.8% of pulmonary TB patients and their sis were extra pulmonary TB patients. From the data analyzed, many TB patients have comorbid diseases, 8.8% of TB patients had positive Diabetes Mellitus status while 1.5% of TB patients had HIV positive.

Table 2. Characteristics of Tuberculosis patients in Semarang City based on data from Tuberculosis Information System (SITB) (N=3434)

Characteristic	Frequency (n)	Percentage (%)
Age (mean; SD)	34.2; 28.9	
Year of Diagnosis		
2020	2282	66.5
2021	1152	33.5
Sex		
Male	1851	53.9
Female	1583	46.1
Employment Status		
Employed	2348	68.4
Unemployed	1086	31.6
Residence Status		
Out of town	775	22.6
In the town	2659	77.4
TB Types		
Pulmonary TB	2810	81.8
Pulmonary Extract TB	624	18.2
Diabetes Mellitus Status		
Positive	301	8.8
Negative	3133	91.2
HIV Status		

Characteristic	Frequency (n)	Percentage (%)
Positive	51	1.5
Negative	3383	98.5
Patient Status		
Treatment failure	120	3.5
Relapse	49	1.4
New Patients	3265	95.1

Patient characteristics, including age (p-value= <0.001), year of diagnosis (p-value= $=0.001$; RR=0.730; 95% CI: 0.603- 0.883), gender (p-value=0.007; RR=1.305; 95% CI=1.076-1.584), employment (p-value=0.013; RR=1.314; 95% CI=1.058-1.631), residence (p-value= <0.001 ; RR =1.503, 95% CI=1.228-1.840), type of TB (p-value=0.013; RR=1.418; 95% CI=1.072-1.874), Diabetes Mellitus (p-value= <0.001 ; RR = 1.852; 95% CI = 1.438-2.385), and patient status (p-value=0.016; RR = 1.537; 95% CI = 1.018-2.321). These characteristics were statistically associated with the incidence of LFTU during TB treatment. In addition, healthcare and social security insurance ownership (p-value= <0.001 ; RR = 0.621; 95% CI = 0.495-0.779), standard treatment (p-value= <0.001 ; RR=1.774; 95% CI=1.389-2.265), close contact examination (p-value=0.018 ; RR=1.859; 95% CI=1.089-3.174), referral status (p-value= <0.001 ; RR=0.574; 95% CI =0.432-0.764), diagnosis method (p-value=0.004; RR=1.344; 95% CI= 1.100-1.643), drugs sources (p-value=0.045; RR:0.285; 95% CI=0.073-1.117) and had a positive significant relationship with the LFTU during TB treatment during the PPM. Detailed data are presented in Table 3.

Table 3. Cross-tabulation predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	Final Result of Treatment				p-Value	RR	95% CI
	LTFU		Recovery				
	n	%	n	%			
Age (mean; SD)	384	11.2	3050	88.8	<0.001	-	6.405-10.825
Year of Diagnosis							
2020	227	9.9	2055	90.1	0.001	0.730	0.603-0.883
2021	157	13.6	995	86.4			
Healthcare and Social Security Agency ownership							
Do not have	88	7.9	1024	92.1	<0.001	0.621	0.495-0.779
Have	296	12.7	2026	87.3			
Treatment Standard							

	Final Result of Treatment				<i>p</i> -Value	RR	95% CI
	LTFU		Recovery				
	n	%	n	%			
Non-standard	64	18.4	284	81.6	<0.001	1.774	1.389-2.265
Standard	320	10.4	2766	89.6			
Sex							
Male	232	12.5	1619	87.5	0.007	1.305	1.076-1.584
Female	152	9.6	1431	90.4			
Employment Status							
Employed	284	12.1	2064	87.9	0.013	1.314	1.058-1.631
Unemployed	100	9.2	986	90.8			
Residence							
Out of town	117	15.1	658	84.9	<0.001	1.503	1.228-1.840
In the town	267	10.0	2392	90.0			
Close Contact Examination							
No	371	11.5	2853	88.5	0.018	1.859	1.089-3.174
Yes	13	6.2	197	93.8			
Referral Status							
Referral	50	7.0	660	93.0	<0.001	0.574	0.432-0.764
Non-referral	334	12.3	2390	87.7			
Diagnose Method							
Clinical	255	12.5	1789	87.5	0.004	1.344	1.100-1.643
Bacteriological	129	9.3	1261	90.7			
TB Types							
Pulmonary TB	332	11.8	2478	88.2	0.013	1.418	1.072-1.874
Pulmonary Extract TB	52	8.3	572	91.7			
Patient Status							
Treatment failure	20	16.7	100	83.3	0.016	0.817	0.413-1.616
Relapse	10	20.4	39	79.6			
New Patients	354	10.8	2911	89.2			
Diabetes Mellitus Status							
Positive	58	19.3	243	80.7	<0.001	1.852	1.438-2.385
Negative	326	10.4	2807	89.6			
HIV Status							
Positive	9	17.6	42	82.4	0.14	1.592	0.873-2.902
Negative	375	11.1	3008	88.9			
Drug Source							
Apart from program	2	3.2	60	96.8	0.045	0.285	0.073-1.117
From program	382	11.3	2990	88.7			

**P*-value<0.05 = significant

The regression analysis was carried out by multivariate analysis (see Table 4). It revealed 4 key variables which became the predictive factors of lost to follow-up status during tuberculosis treatment during the PPM. The variables are year of diagnose (AOR=1.541; *p*-value=<0.001; 95% CI=1.228-1.934), referral status (AOR=1.562, *p*-value=0.007; 95% CI=1.130-2.160), healthcare and social security insurance ownership (AOR=1.638; *p*-

value= <0.001 ; 95% CI=1.263-2.124, and drugs sources (AOR=4.667; p-value=0.035; 95% CI=1.117-19489).

Table 4. Logistic Regression predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	<i>P</i> -Value	Adjusted OR	95%CI
Year of Diagnosis	<0.001	1.541	1.228-1.934
Referral Status	0.007	1.562	1.130-2.160
Healthcare and Social Security Agency Ownership	<0.001	1.638	1.263-2.124
Drug Source	0.035	4.667	1.117-19.489

Discussion

The national strategy of TB Control Program aims at providing universal access to quality TB services through a systematic Find Cure Until Heal (TOSS) activity for all TB patients supported by active participation of health care providers both in public and private sectors[5,12,13]. The PPM involves all health care facilities to expand TB patient services and the continuity of a comprehensive TB control program. One of the objectives is to prevent LTFU patients during TB treatment[5,12]. Most health facilities in Semarang, both private and public, have contributed to TB reporting. In practice, government health facilities (hospitals and primary healthcare center) have reported more cases than private hospitals.

The logistic regression analysis revealed three key factors that influenced the work of LTFU in tuberculosis patients during the PPM period: the patient was referral, the patient did not have any healthcare and social security insurance, and the medication received was not a program drug. According to this study, the most significant factor influencing the incidence of LTFU during the PPM period is patients who receive drug sources other than the program, with 4.6 times probability. These findings suggest that patients tend to use complementary medicine. Previous research has shown that in general, Asians use complementary medicine in addition to conventional medicine[14]. In addition, community's influence plays a strong role in TB medication in Asia. Accessibility, tradition or belief, and feelings of dissatisfaction with

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3 conventional drugs are all factors that encourage the use of alternative drugs. Another factor
4 that affects LTFU with 1.5 times probability is referral patients[15]. Research in Pakistan shows
5 that patients who undergo treatment at referral health facilities and become referral patients are
6 more likely to experience LTFU before starting TB treatment[16]. This is due to the distance
7 between the patient's residence and the facility. The greater the distance, the higher the LTFU
8 rate, particularly for patients living outside the city[17].
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17 Because treatment is not cheap and takes a long time, health insurance is essential for
18 TB patients in Indonesia, who are mostly from lower-middle-class families. TB patients'
19 treatment costs more because they must pay for co-morbidity medication, transportation, and
20 accommodation[18]. Furthermore, the indirect costs of TB treatment the patients have to endure
21 are reduced income or a lower proportion of household income, which can lead to deeper
22 poverty. According to previous research, the costs incurred when a person does not work while
23 on treatment account for 67% of the total costs incurred by TB patients[19].
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33 The results of the study, which found that patients without health insurance had a 1.6
34 times greater likelihood of missing treatment, were relevant to previous studies because having
35 health insurance ensures that TB patients do not incur personal costs for care and treatment until
36 they are declared cured. The availability of health insurance is critical, particularly in cases of
37 TB with complications or additional conditions such as diabetes, hypertension, impaired kidney
38 function, pregnancy and lactation, or other diseases that necessitate additional examination and
39 treatment. Patients without health insurance must still pay for additional examinations,
40 hospitalization, or other drugs not covered by the government's TB program. Due to the high
41 costs, TB patients, particularly those without health insurance, are more likely to be absent or
42 to discontinue treatment[20].
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55 LTFU factors in TB patients should be better understood for a better understanding of
56 treatment adherence challenges, especially during the PPM initiative. As a result, we
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2
3 recommend a qualitative study to assess other factors that increase the risk of LTFU that are
4 reviewed in cross-sectoral services and support, particularly private health facilities in the PPM
5 period, and how health workers treat LTFU patients. One limitation of this study is that we
6 assessed LTFU using electronic records at the SITB rather than actively tracking patients.
7
8 Furthermore, there is no access to a list of LTFU patients at facilities located outside of
9 Semarang City, so it is possible that some TB patients have transferred treatment to locations
10 outside of the city but are still classified as LTFU. However, as these patients represented only
11 11.2% of all patients in this study, this factor is unlikely to have had much effect on the overall
12 outcome. Another limitation is that because the data is secondary, we were unable to determine
13 the exact factors for LTFU from the patient's perspective. Despite these limitations, this study
14 extends our understanding of the factors that contribute to LTFU during TB treatment during
15 the PPM initiative. The TB control program manager can use this information as key reference
16 to optimize the implementation of PPM in the context of TB control.
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35 **Acknowledgements**

36
37 The author would like to thank all team members of this research. This study is supported by
38 Health Office of Semarang City and Universitas Negeri Semarang, Indonesia.
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44 **Competing Interests**

45
46 The authors declares that they have no competing interests with regards to authorship and/or
47 publication of this article.
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54 **Author's Contribution**

55
56 All authors contributed to the study conception and design. SRR: conceptualization,
57 methodology, writing review and editing draft; MSS: conceptualization, project administration
58
59
60

1
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3 writing review and editing draft; MZS: data curation, formal analysis, methodology,
4 writing original draft; MA: methodology and writing original draft; FI: data curation and
5 formal analysis; MS: project administration and supervision; DM: conceptualization and formal
6 formal analysis; BDS: methodology and project administration; SD: data curation and formal analysis;
7 ANM: conceptualization, data curation, formal analysis, methodology, review & editing; RA:
8 formal analysis and project administration; MDA: conceptualization, project administration and
9 resources; NW: data curation, writing review & editing; I: formal analysis, review & editing;
10 ADW: investigation and project administration; AKL: formal analysis and investigation;
11 ZM: formal analysis, methodology, writing review & editing. All authors read and approved
12 the final manuscript.
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Table 1. Characteristics of health facilities at the research site

Type of Health Facilities	Number of health facilities reporting TB	Total of health facilities	%
Primary Healthcare Center	37	37	100
Public Hospitals	8	8	100
Private Hospitals	19	21	90.5
Community Pulmonary Health Center	1	1	100
Average			97.6

For Review Only

Table 2. Characteristics of Tuberculosis patients in Semarang City based on data from Tuberculosis Information System (SITB) (N=3434)

Characteristic	Frequency (n)	Percentage (%)
Age (mean; SD)	34.2; 28.9	
Year of Diagnosis		
2020	2282	66.5
2021	1152	33.5
Sex		
Male	1851	53.9
Female	1583	46.1
Employment Status		
Employed	2348	68.4
Unemployed	1086	31.6
Residence Status		
Out of town	775	22.6
In the town	2659	77.4
TB Types		
Pulmonary TB	2810	81.8
Pulmonary Extract TB	624	18.2
Diabetes Mellitus Status		
Positive	301	8.8
Negative	3133	91.2
HIV Status		
Positive	51	1.5
Negative	3383	98.5
Patient Status		
Treatment failure	120	3.5
Relapse	49	1.4
New Patients	3265	95.1

Table 3. Cross-tabulation predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	Final Result of Treatment				<i>p</i> -Value	RR	95% CI
	LTFU		Recovery				
	n	%	n	%			
Age (mean; SD)	384	11.2	3050	88.8	<0.001	-	6.405-10.825
Year of Diagnosis							
2020	227	9.9	2055	90.1	0.001	0.730	0.603-0.883
2021	157	13.6	995	86.4			
Healthcare and Social Security Agency ownership							
Do not have	88	7.9	1024	92.1	<0.001	0.621	0.495-0.779
Have	296	12.7	2026	87.3			
Treatment Standard							
Non-standard	64	18.4	284	81.6	<0.001	1.774	1.389-2.265
Standard	320	10.4	2766	89.6			
Sex							
Male	232	12.5	1619	87.5	0.007	1.305	1.076-1.584
Female	152	9.6	1431	90.4			
Employment Status							
Employed	284	12.1	2064	87.9	0.013	1.314	1.058-1.631
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In the town	267	10.0	2392	90.0			
Close Contact Examination							
No	371	11.5	2853	88.5	0.018	1.859	1.089-3.174
Yes	13	6.2	197	93.8			
Referral Status							
Referral	50	7.0	660	93.0	<0.001	0.574	0.432-0.764
Non-referral	334	12.3	2390	87.7			
Diagnose Method							
Clinical	255	12.5	1789	87.5	0.004	1.344	1.100-1.643
Bacteriological	129	9.3	1261	90.7			
TB Types							
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Diabetes Mellitus Status							
Positive	58	19.3	243	80.7	<0.001	1.852	1.438-2.385
Negative	326	10.4	2807	89.6			
HIV Status							
Positive	9	17.6	42	82.4	0.14	1.592	0.873-2.902
Negative	375	11.1	3008	88.9			
Drug Source							
Apart from program	2	3.2	60	96.8	0.045	0.285	0.073-1.117
From program	382	11.3	2990	88.7			

**P*-value<0.05 = significant

Table 4. Logistic Regression predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	<i>P</i> -Value	Adjusted OR	95%CI
Year of Diagnosis	<0.001	1.541	1.228-1.934
Referral Status	0.007	1.562	1.130-2.160
Healthcare and Social Security Agency Ownership	<0.001	1.638	1.263-2.124
Drug Source	0.035	4.667	1.117-19.489

For Review Only

Ethiopian Journal of Health Sciences

Decision Letter (EJHS-2022-0702)

From: kasechab@gmail.com

To: sriratnarahayu@mail.unnes.ac.id

CC:

Subject: Ethiopian Journal of Health Sciences - Decision on Manuscript ID EJHS-2022-0702

Body: 01-Aug-2022

Dear Mrs. Rahayu:

Manuscript ID EJHS-2022-0702 entitled "Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia" which you submitted to the Ethiopian Journal of Health Sciences, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some MAJOR revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments POINT-BY-POINT and revise your manuscript.

To revise your manuscript, log into <https://mc.manuscriptcentral.com/ju-ejhs> and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You may also click the below link to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

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You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Ethiopian Journal of Health Sciences, your revised manuscript should be submitted by The author due date is unavailable. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Ethiopian Journal of Health Sciences and I look forward to receiving your revision.

Sincerely,
Prof. Abraham Haileamlak
Associate Editor, Ethiopian Journal of Health Sciences
kasechab@gmail.com

Reviewer(s)' Comments to Author:
Reviewer: 1

Comments to the Author
Well-designed articles. We found that there were a few things that needed to be added to improve the article.

Reviewer: 2

Comments to the Author

Dear Editor, thank you very much for inviting me to review this important article. It is a relevant article to public health practice. I had a hard time however that the manuscript does not have line numbers to easily associate comments to texts in the document.

Page 1 of 15

Abstract

Abstract

Results

In the factors identified to affect LTFU what does 'drugs source' refers to? The authors need to clear confusion on this important variable.

Conclusion: The statement, "... who receive TB treatment rather than program drugs" that the authors suggested on the PPM in dealing with LTFU is not clear.

Page 1 of 15

Introduction

The authors presented the objective and central principle of Public Private Mix (PPM). It would be good if the authors added more clarity on what the PPM refers to with some definition plus a few details on its functionality.

Page 2 of 15

Introduction

First paragraph

The statement in this second paragraph on page 2 is not clear enough as the private sector is said to cover 42% and at the same time this same sector (represented by private clinics and hospitals) covers only 1 and 8% respectively. The authors need to add clarity on this too.

Paragraph 2 of 15

The third paragraph (the introduction in its entirety) in the introduction section should be better moved to somewhere in the methods section.

Introduction

General:

The authors have tried to present the problem in context. However, no effort was made to summarize factors associated with LTFU from previous literature. Whether there has been an effort to reduce LTFU in the Indonesian context as they found that 'year of diagnosis' had a significant association with LTFU. I think it is good if the authors add a few details on these.

Page 3 of 15

Methods

Study setting

The authors should add more details about PPM here

I think certain important points seem to be missing:

- Population studied
- Eligibility
- Sample size
- Sampling technique
- Variable measurement

>>The authors should add a few details on the above points

Independent variables:

Listing independent variables without a few descriptions of how they are measured do not clear confusion. The authors should add more to this.

Page 4 of 15

Methods

Statistical analysis:

What is 'derivation cohort' stated in this section?

Statistical analysis:

How is LTFU measured (before Rx initiation or after or both) when was a patient declared LTFU from TB care)? What is the outcome level? This has to be well stated to judge the appropriateness of the model used.

Also, use the expanded and abbreviated forms consistently across the document. E.g. LTFU is in its expanded form in this section.

Ethical approval

Journals require authors to mention that the research is conducted as per certain ethical guidelines, e.g. the Helsinki Declaration. Kindly mention waiver of consent, confidentiality...

Results

Page 4 of 15

Results

Results should have better presented with some subheadings

The first three lines of the results section should better be presented under the study settings section in the methods.

Page 5 of 15

To what does the word 'sis' in the statement starting with "As many as 81.8% of pulmonary TB patients and their sis were extra pulmonary TB patients," refers?

Page 5 of 15; 2nd paragraph

Correct the reporting of the order of estimates for a variable as effect size, CI, and P-value.

Is it not enough to report effect sizes in just two decimal places?

Maybe better if protective factors and factors that increase LTFU are presented separately than as it is presented in a mixed way here.

The factors associated with LTFU lack clarity in the category coding. For example, if you take diabetes mellitus, was it the presence or absence that predicts LTFU? Similar questions for the other factors too, which gender is associated with an increase in LTFU...?

Page 5 of 15

Effect estimates are also presented in the second paragraph on this page. Why this third paragraph is needed if it presents the same regression output?

Often interpretations of results are reserved to outputs from the multiple regression models.

Page 6 of 15

Discussion

The first paragraph of the discussion should preferably present a summary of key findings that addressed study objectives.

Paragraphs that follow should expand on explaining key findings presented in the study.

Interpretations should oversee public health practice, and policy implications, and indicate cautions on the application of study findings.

Reviewer: 3

Comments to the Author

1. Introduction

Page 1, line 49-50: Please add with an more explanation about PPM.

Page 2, line 21-22: in the sentence "However, only 32% of cases are recorded...". It is better to make it clearer. Does it refer to cases in private health facilities or all cases in Indonesia (public and private health facilities)?

Page 2, line 44-45: I think it is better if you change the word "development" with other suitable word.

2. Methods

Page 3, line 33-34: Please check again the definition of LTFU in the methods (in dependent variable) and in the introduction (Page 2, line 37-38)

Give more explanation regarding the variables, e.g. the scale of measurements.

Page 4, line 14-15: which one did you use for logistic regression? Backward, forward or automatic method?


3. Results

Page 5, line 9-22: the sentence is not complete and too long.

Date Sent: 01-Aug-2022

Files attached

[Review for Lost to Follow up among TB.pdf](#)

 Close Window



Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia

Journal:	<i>Ethiopian Journal of Health Sciences</i>
Manuscript ID	EJHS-2022-0702
Manuscript Type:	Original Article
Keyword:	Health Facilities, Lost to Follow-Up, Tuberculosis < Infectious diseases, Indonesia

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Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia

Abstract

Background: Indonesia's national Tuberculosis (TB) strategy is public-private mix (PPM). The PPM aims to treat patients who have lost sight during TB treatment as these patients are TB carriers and at risk of transmitting TB. The purpose of this study was to identify predictive factors for loss to follow-up (LFTU) among TB patients receiving treatment when the PPM was at place in Indonesia.

Methods: The design of this study was a retrospective cohort study. The data used in this study was sourced from the Tuberculosis Information System (SITB) of Semarang which was recorded routinely during 2020-2021. Univariate analysis, crosstabulation, and logistic regression were performed on 3434 TB patients meeting the minimum variables.

Results: The participation of health facilities in reporting TB during the PPM era in Semarang reached 97.6% consisting of 37 primary healthcare center (100%), 8 public hospitals (100%), 19 private hospitals (90.5%), and a community-based pulmonary health center (100%). The regression analysis reveal that the predictive factors of LTFU-TB during the PPM are the year of diagnosis (AOR=1.541; p-value=<0.001; 95% CI=1.228-1.934), referral status (AOR=1.562, p-value=0.007; 95% CI=1.130-2160), healthcare and social security insurance ownership (AOR=1.638; p-value=<0.001; 95% CI=1.263-2.124), drugs source (AOR=4.667; p-value=0.035; 95% CI=1.117-19.489).

Conclusions: The PPM strategy in dealing with LTFU patients should focus on TB patients without Healthcare and Social Security Insurance and who receive TB treatment rather than program drugs.

Keywords: Health Facilities, Lost to Follow-Up, Tuberculosis, Indonesia

Introduction

Tuberculosis (TB) is an infectious disease that remains a major health problem worldwide. In 2019, the number of people diagnosed and confirmed TB cases reached 7.1 million globally (1). World Health Organization (WHO) estimates that there is a 2.9-million gap between the number of diagnosed TB cases and the number of notified cases due to the high unreported cases. One country that accounts for more than half of the global gap is Indonesia (10%) (2). Indonesia's national TB strategy is public-private mix (PPM) which primarily aims to increase TB case detection (3,4). The case network is one of the PPM network's principles, namely the continuity of treatment of TB patients from referrals/transfers and the tracking of TB patients who are lost to follow-up (5).

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3 The PPM approach is to ensure equitable, quality, and sustainable access to TB services
4 for those affected by TB (universal access) in ensuring TB patients' recovery. However, within
5 the Indonesian context, private sector involvement remains low (4). According to Indonesia
6 National Development Planning Agency, the private sector manages more than 50% of
7 hospitals, provides 60% of outpatient care, and 43% of hospitals with inpatients (4,6). The
8 Patient Pathway Analysis (PPA) study in 2017 revealed that 54% of the discovery and treatment
9 of TB has been carried out by government health facilities, and 42% by the private sector.
10 Private health facilities such as private clinics contribute only 1%, while private hospitals
11 contribute 8% (7). However, only 32% of cases are recorded, indicating that 68% of cases go
12 unreported. Most of these missing cases are believed to be in the private sector and go
13 unreported, even though some of them can receive both diagnosis and treatment at the same
14 time.

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31 The success of tuberculosis control in Indonesia can be described by three indicators.
32 They are complete treatment rate (% complete rate), cure rate (% cure rate), and treatment
33 success rate (% success rate). TB patients are therefore classified as cured, completed treatment,
34 failed treatment, lost to follow-up, or died based on the outcome of their treatment. Lost to
35 follow-up (LTFU) was defined as patients who received treatment for at least 4 weeks and the
36 treatment was discontinued for more than eight consecutive weeks (8).

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45 One of the reasons for the development of acquired Drug Resistance Tuberculosis (DR-
46 TB) is LTFU. Patients who are readmitted after LTFU are more likely to redevelop infectious
47 active TB and are at higher risk of developing further drug resistant strains of tuberculosis
48 (9,10). According to reports on the economic challenges of TB drug non-adherence, an
49 estimated 52 MDR-TB patients lost to follow-up resulted in 5 patients developing XDR-TB, 3
50 newly infected MDR-TB and a new XDR-TB, and 3 deaths (11).

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3 LTFU can increase the risk of clinical deterioration, treatment failure, and further
4 complications in tuberculosis patients. Patients who discontinue treatment too early are one of
5 the leading causes of treatment failure (11). The dropout rate is critical because low LTFU as a
6 result of improved TB management will reduce re-treatment case by 10-20% in the coming
7 years (5). This issue highlights the importance to study the predictors of LTFU during the PPM.
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17 **Methods**

18 *Study design and data source*

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20 The design of this study was a retrospective cohort study. This study integrates data from the
21 Tuberculosis Information System (SITB) via the TB03 form provided by the Ministry of
22 Health. This system summarizes tuberculosis patient data and treatment monitoring. The
23 research data is collected from 2020 to mid-2021.
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30 *Data Management and Analysis*

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33 **Dependent variable:** Patients whose tuberculosis treatment status was lost to follow-up were
34 defined as discontinuing treatment for two or more consecutive months (8 weeks) for any reason
35 without medical consent (11).
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40 **Independent variables:** The independent variables that are fully recorded in the SITB and can
41 be included in the final analysis are the year of diagnosis, which is classified as 2020 or 2021
42 (January - July), healthcare and social security insurance ownership; standard of treatment;
43 gender; employment status; place of residence, which is classified as within the city of
44 Semarang or outside the city of Semarang; close contact examination, which we classify as
45 close contact examination is carried out or not carried out; and referral status which is classified
46 as referral patients or patients who come to health services on their own for TB tests; diagnostic
47 methods; types of TB; patient status; Diabetes Mellitus status; HIV Status; and drugs source,
48 which is classified as program drugs or drugs obtained outside of the program.
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Statistical Analysis

Based on variable categories, data is presented in terms of frequency and percentage. For the derivation cohort, bivariate analysis was used to identify risk factors associated with loss to follow-up, comparing subjects who recovered plus subjects who completed treatment with subjects who were lost to follow-up. To determine predictors of loss to follow-up, multivariable analysis was performed using logistic regression test. The patients with the lowest loss to follow-up were designated as the reference group. *P*-values of 0.05 or less were considered statistically significant.

Ethical approval

The Health Research Ethics Committee of Universitas Negeri Semarang has reviewed and approved the protocol by issuing a letter numbered 095/KEPK/EC/2021.

Results

Health facilities in Semarang City consist of primary healthcare center, public and private hospitals, community pulmonary health center, as well as independent practice doctors and clinics which are reported through primary healthcare center and hospitals as referral health facilities. All 37 primary healthcare center in Semarang (100%) participated in reporting and recording TB cases. Likewise, 8 public hospitals and a primary healthcare center, all of them (100%) participated in the reporting and recording TB cases. However, out of 21 private hospitals in Semarang, only 90.5% private hospitals participated in reporting and recording TB cases. Detailed data are presented in Table 1.

Characteristics of respondents based on Tuberculosis Information System (SITB) data are presented in Table 2. The average age of TB patients is 34.2 years old (SD: 28.9), with male patients (53.9%) outnumbering female patients. Most of them live in Semarang (77.4%), while the rest live in other neighboring cities. As many as 81.8% of pulmonary TB patients and their

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3 sis were extra pulmonary TB patients. From the data analyzed, many TB patients have comorbid
4 diseases, 8.8% of TB patients had positive Diabetes Mellitus status while 1.5% of TB patients
5 had HIV positive.
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10 Patient characteristics, including age (p-value= <0.001), year of diagnosis (p-value
11 = 0.001 ; RR=0.730; 95% CI: 0.603- 0.883), gender (p-value=0.007; RR=1.305; 95% CI=1.076-
12 1.584), employment (p-value=0.013; RR=1.314; 95% CI=1.058-1.631), residence (p-
13 value= <0.001 ; RR =1.503, 95% CI=1.228-1.840), type of TB (p-value=0.013; RR=1.418; 95%
14 CI=1.072-1.874), Diabetes Mellitus (p-value= <0.001 ; RR = 1.852; 95% CI = 1.438-2.385), and
15 patient status (p-value=0.016; RR = 1.537; 95% CI = 1.018-2.321). These characteristics were
16 statistically associated with the incidence of LFTU during TB treatment. In addition, healthcare
17 and social security insurance ownership (p-value= <0.001 ; RR = 0.621; 95% CI = 0.495-0.779),
18 standard treatment (p-value= <0.001 ; RR=1.774; 95% CI=1.389-2.265), close contact
19 examination (p-value=0.018 ; RR=1.859; 95% CI=1.089-3.174), referral status (p-
20 value= <0.001 ; RR=0.574; 95% CI =0.432-0.764), diagnosis method (p-value=0.004;
21 RR=1.344; 95% CI= 1.100-1.643), drugs sources (p-value=0.045; RR:0.285; 95% CI=0.073-
22 1.117) and had a positive significant relationship with the LFTU during TB treatment during
23 the PPM. Detailed data are presented in Table 3.
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42 The regression analysis was carried out by multivariate analysis (see Table 4). It revealed
43 4 key variables which became the predictive factors of lost to follow-up status during
44 tuberculosis treatment during the PPM. The variables are year of diagnose (AOR=1.541; p-
45 value= <0.001 ; 95% CI=1.228-1.934), referral status (AOR=1.562, p-value=0.007; 95%
46 CI=1.130-2.160), healthcare and social security insurance ownership (AOR=1.638; p-
47 value= <0.001 ; 95% CI=1.263-2.124, and drugs sources (AOR=4.667; p-value=0.035; 95%
48 CI=1.117-19489).
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Discussion

The national strategy of TB Control Program aims at providing universal access to quality TB services through a systematic Find Cure Until Heal (TOSS) activity for all TB patients supported by active participation of health care providers both in public and private sectors (5,12,13). The PPM involves all health care facilities to expand TB patient services and the continuity of a comprehensive TB control program. One of the objectives is to prevent LTFU patients during TB treatment (5,12). Most health facilities in Semarang, both private and public, have contributed to TB reporting. In practice, government health facilities (hospitals and primary healthcare center) have reported more cases than private hospitals.

The logistic regression analysis revealed three key factors that influenced the work of LTFU in tuberculosis patients during the PPM period: the patient was referral, the patient did not have any healthcare and social security insurance, and the medication received was not a program drug. According to this study, the most significant factor influencing the incidence of LTFU during the PPM period is patients who receive drug sources other than the program, with 4.6 times probability. These findings suggest that patients tend to use complementary medicine. Previous research has shown that in general, Asians use complementary medicine in addition to conventional medicine (14). In addition, community's influence plays a strong role in TB medication in Asia. Accessibility, tradition or belief, and feelings of dissatisfaction with conventional drugs are all factors that encourage the use of alternative drugs. Another factor that affects LTFU with 1.5 times probability is referral patients (15). Research in Pakistan shows that patients who undergo treatment at referral health facilities and become referral patients are more likely to experience LTFU before starting TB treatment (16). This is due to the distance between the patient's residence and the facility. The greater the distance, the higher the LTFU rate, particularly for patients living outside the city (17).

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3 Because treatment is not cheap and takes a long time, health insurance is essential for
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5 TB patients in Indonesia, who are mostly from lower-middle-class families. TB patients'
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7 treatment costs more because they must pay for co-morbidity medication, transportation, and
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9 accommodation (18). Furthermore, the indirect costs of TB treatment the patients have to
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11 endure are reduced income or a lower proportion of household income, which can lead to deeper
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13 poverty. According to previous research, the costs incurred when a person does not work while
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15 on treatment account for 67% of the total costs incurred by TB patients (19).
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19 The results of the study, which found that patients without health insurance had a 1.6
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21 times greater likelihood of missing treatment, were relevant to previous studies because having
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23 health insurance ensures that TB patients do not incur personal costs for care and treatment until
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25 they are declared cured. The availability of health insurance is critical, particularly in cases of
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27 TB with complications or additional conditions such as diabetes, hypertension, impaired kidney
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29 function, pregnancy and lactation, or other diseases that necessitate additional examination and
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31 treatment. Patients without health insurance must still pay for additional examinations,
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33 hospitalization, or other drugs not covered by the government's TB program. Due to the high
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35 costs, TB patients, particularly those without health insurance, are more likely to be absent or
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37 to discontinue treatment (20).
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42 LTFU factors in TB patients should be better understood for a better understanding of
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44 treatment adherence challenges, especially during the PPM initiative. As a result, we
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46 recommend a qualitative study to assess other factors that increase the risk of LTFU that are
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48 reviewed in cross-sectoral services and support, particularly private health facilities in the PPM
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50 period, and how health workers treat LTFU patients. One limitation of this study is that we
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52 assessed LTFU using electronic records at the SITB rather than actively tracking patients.
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54 Furthermore, there is no access to a list of LTFU patients at facilities located outside of
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56 Semarang City, so it is possible that some TB patients have transferred treatment to locations
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3 outside of the city but are still classified as LTFU. However, as these patients represented only
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5 11.2% of all patients in this study, this factor is unlikely to have had much effect on the overall
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7 outcome. Another limitation is that because the data is secondary, we were unable to determine
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9 the exact factors for LTFU from the patient's perspective. Despite these limitations, this study
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11 extends our understanding of the factors that contribute to LTFU during TB treatment during
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13 the PPM initiative. The TB control program manager can use this information as key reference
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15 to optimize the implementation of PPM in the context of TB control.
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22
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24
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30 **Competing Interests**

31
32 The authors declares that they have no competing interests with regards to authorship and/or
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34 publication of this article.
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40 **Author's Contribution**

41
42 All authors contributed to the study conception and design. SRR: conceptualization,
43
44 methodology, writing review and editing draft; MSS: conceptualization, project administration
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46 writing review and editing draft; MZS: data curation, formal analysis, methodology,
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48 writing original draft; MA: methodology and writing original draft; FI: data curation and
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50 formal analysis; MS: project administration and supervision; DM: conceptualization and formal
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52 analysis; BDS: methodology and project administration; SD: data curation and formal analysis;
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54 ANM: conceptualization, data curation, formal analysis, methodology, review & editing; RA:
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56 formal analysis and project administration; MDA: conceptualization, project administration and
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3 resources; NW: data curation, writing review & editing; I: formal analysis, review & editing;
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5 ADW: investigation and project administration; AKL: formal analysis and investigation;
6
7 ZM: formal analysis, methodology, writing review & editing. All authors read and approved
8
9 the final manuscript.
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Table 1. Characteristics of health facilities at the research site

Type of Health Facilities	Number of health facilities reporting TB	Total of health facilities	%
Primary Healthcare Center	37	37	100
Public Hospitals	8	8	100
Private Hospitals	19	21	90.5
Community Pulmonary Health Center	1	1	100
Average			97.6

For Review Only

Table 2. Characteristics of Tuberculosis patients in Semarang City based on data from Tuberculosis Information System (SITB) (N=3434)

Characteristic	Frequency (n)	Percentage (%)
Age (mean; SD)	34.2; 28.9	
Year of Diagnosis		
2020	2282	66.5
2021	1152	33.5
Sex		
Male	1851	53.9
Female	1583	46.1
Employment Status		
Employed	2348	68.4
Unemployed	1086	31.6
Residence Status		
Out of town	775	22.6
In the town	2659	77.4
TB Types		
Pulmonary TB	2810	81.8
Pulmonary Extract TB	624	18.2
Diabetes Mellitus Status		
Positive	301	8.8
Negative	3133	91.2
HIV Status		
Positive	51	1.5
Negative	3383	98.5
Patient Status		
Treatment failure	120	3.5
Relapse	49	1.4
New Patients	3265	95.1

Table 3. Cross-tabulation predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	Final Result of Treatment				<i>p</i> -Value	RR	95% CI
	LTFU		Recovery				
	n	%	n	%			
Age (mean; SD)	384	11.2	3050	88.8	<0.001	-	6.405-10.825
Year of Diagnosis							
2020	227	9.9	2055	90.1	0.001	0.730	0.603-0.883
2021	157	13.6	995	86.4			
Healthcare and Social Security Agency ownership							
Do not have	88	7.9	1024	92.1	<0.001	0.621	0.495-0.779
Have	296	12.7	2026	87.3			
Treatment Standard							
Non-standard	64	18.4	284	81.6	<0.001	1.774	1.389-2.265
Standard	320	10.4	2766	89.6			
Sex							
Male	232	12.5	1619	87.5	0.007	1.305	1.076-1.584
Female	152	9.6	1431	90.4			
Employment Status							
Employed	284	12.1	2064	87.9	0.013	1.314	1.058-1.631
Unemployed	100	9.2	986	90.8			
Residence							
Out of town	117	15.1	658	84.9	<0.001	1.503	1.228-1.840
In the town	267	10.0	2392	90.0			
Close Contact Examination							
No	371	11.5	2853	88.5	0.018	1.859	1.089-3.174
Yes	13	6.2	197	93.8			
Referral Status							
Referral	50	7.0	660	93.0	<0.001	0.574	0.432-0.764
Non-referral	334	12.3	2390	87.7			
Diagnose Method							
Clinical	255	12.5	1789	87.5	0.004	1.344	1.100-1.643
Bacteriological	129	9.3	1261	90.7			
TB Types							
Pulmonary TB	332	11.8	2478	88.2	0.013	1.418	1.072-1.874
Pulmonary Extract TB	52	8.3	572	91.7			
Patient Status							
Treatment failure	20	16.7	100	83.3	0.016	ref.	ref.
Relapse	10	20.4	39	79.6			
New Patients	354	10.8	2911	89.2			
Diabetes Mellitus Status							
Positive	58	19.3	243	80.7	<0.001	1.852	1.438-2.385
Negative	326	10.4	2807	89.6			
HIV Status							
Positive	9	17.6	42	82.4	0.14	1.592	0.873-2.902
Negative	375	11.1	3008	88.9			
Drug Source							
Apart from program	2	3.2	60	96.8	0.045	0.285	0.073-1.117
From program	382	11.3	2990	88.7			

**P*-value<0.05 = significant

Table 4. Logistic Regression predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	<i>P</i> -Value	Adjusted OR	95%CI
Year of Diagnosis	<0.001	1.541	1.228-1.934
Referral Status	0.007	1.562	1.130-2.160
Healthcare and Social Security Agency Ownership	<0.001	1.638	1.263-2.124
Drug Source	0.035	4.667	1.117-19.489

For Review Only

Ethiopian Journal of Health Sciences

Decision Letter (EJHS-2022-0702.R1)**From:** kasechab@gmail.com**To:** sriratnarahayu@mail.unnes.ac.id**CC:****Subject:** Ethiopian Journal of Health Sciences - Decision on Manuscript ID EJHS-2022-0702.R1**Body:** 12-Sep-2022

Dear Mrs. Rahayu:

Manuscript ID EJHS-2022-0702.R1 entitled "Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia" which you submitted to the Ethiopian Journal of Health Sciences, has been reviewed. The comments of the EDITOR(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but EDITOR suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer AND EDITOR(s)' comments and revise your manuscript.

To revise your manuscript, log into <https://mc.manuscriptcentral.com/ju-ejhs> and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You may also click the below link to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Ethiopian Journal of Health Sciences, your revised manuscript should be submitted by The author due date is unavailable. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Ethiopian Journal of Health Sciences and I look forward to receiving your revision.

Sincerely,
Prof. Abraham Haileamlak
Associate Editor, Ethiopian Journal of Health Sciences
kasechab@gmail.com

Reviewer(s)' Comments to Author:
Reviewer: 1

Comments to the Author
Dear Authors,
Thank you for revising properly based on my comments.

Reviewer: 2

Comments to the Author


I thank the editor for inviting me to review this interesting paper.

I thank the authors for taking the time to correct the manuscript. I see the manuscript has substantial improvement from the previous submission but I couldn't confirm that all my comments have been addressed as there was no attached file as a response to the reviewer.

EDITOR'S NOTE

1. PLEASE MAKE A THOROUGH LANGUAGE EDITION
2. WE ENCOURAGE TO CITE RELEVANT ARTICLE/S PUBLISHED ON EJHS. THERE ARE PLENTY OF PUBLISHED ARTICLES ON EJHS ABOUT TUBERCULOSIS
3. THEN, PUT ALL PUBLISHABLE COMPONENTS (TITLE PAGE WITH THEIR AFFILIATION, DATE OF SUBMISSION, DATE OF ACCEPTANCE (TODAY), THE ABSTRACT, MAIN DOCUMENT, TABLE AND FIGURE) OF THE MANUSCRIPT TOGETHER AS ONE FILE AND SUBMIT BACK.

Date Sent: 12-Sep-2022

 Close Window



Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia

Journal:	<i>Ethiopian Journal of Health Sciences</i>
Manuscript ID	EJHS-2022-0702.R1
Manuscript Type:	Original Article
Keyword:	Health Facilities, Lost to Follow-Up, Tuberculosis < Infectious diseases, Indonesia

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Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia

Abstract

Background: Indonesia's national Tuberculosis (TB) strategy is public-private mix (PPM). The PPM aims to treat patients who have lost sight during TB treatment as these patients are TB carriers and at risk of transmitting TB. The purpose of this study was to identify predictive factors for loss to follow-up (LFTU) among TB patients receiving treatment when the PPM was at place in Indonesia.

Methods: The design of this study was a retrospective cohort study. The data used in this study was sourced from the Tuberculosis Information System (SITB) of Semarang which was recorded routinely during 2020-2021. Univariate analysis, crosstabulation, and logistic regression were performed on 3434 TB patients meeting the minimum variables.

Results: The participation of health facilities in reporting TB during the PPM era in Semarang reached 97.6% consisting of 37 primary healthcare center (100%), 8 public hospitals (100%), 19 private hospitals (90.5%), and a community-based pulmonary health center (100%). The regression analysis reveal that the predictive factors of LTFU-TB during the PPM are the year of diagnosis (AOR=1.541; p-value=<0.001; 95% CI=1.228-1.934), referral status (AOR=1.562, p-value=0.007; 95% CI=1.130-2160), healthcare and social security insurance ownership (AOR=1.638; p-value=<0.001; 95% CI=1.263-2.124), drugs source (AOR=4.667; p-value=0.035; 95% CI=1.117-19.489).

Conclusions: The PPM strategy in dealing with LTFU patients should focus on TB patients without Healthcare and Social Security Insurance and who receive TB treatment rather than program drugs.

Keywords: Health Facilities, Lost to Follow-Up, Tuberculosis, Indonesia

Introduction

Tuberculosis (TB) is an infectious disease that remains a major health problem worldwide. In 2019, the number of people diagnosed and confirmed TB cases reached 7.1 million globally (1). World Health Organization (WHO) estimates that there is a 2.9-million gap between the number of diagnosed TB cases and the number of notified cases due to the high unreported cases. One country that accounts for more than half of the global gap is Indonesia (10%) (2). WHO global policy for TB control is to involve all service providers through a Public-Private Mix (PPM) approach (1,3). The goal of PPM is to improve case detection and treatment success that contributes to missing cases (4,5). The target providers are not only private and corporate sector (hospitals or institutions, private practitioners), and voluntary sector (non-government organization or community-based organizations), but also

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3 public sector itself (many types of public providers such as general) and speciality hospitals,
4 teaching hospitals, prisons, military-owned providers and others who have not joined the
5 program (5,6). The case network is one of the PPM network's principles, namely the continuity
6 of treatment of TB patients from referrals/transfers and the tracking of TB patients who are lost
7 to follow-up (7).
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14 This policy has also been adopted by the Government of Indonesia. Research evidence in
15 India and Myanmar shows that PPM strengthens TB care and control (8). Research in Pakistan
16 shows that Among the PPM approaches, general practitioners and non-governmental
17 organization facilities achieve 94-95% treatment success; private hospitals achieved 82%
18 success (9)
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26 The PPM approach is to ensure equitable, quality, and sustainable access to TB services
27 for those affected by TB (universal access) in ensuring TB patients' recovery. However, within
28 the Indonesian context, private sector involvement remains low (10). According to Indonesia
29 National Development Planning Agency, the private sector manages more than 50% of
30 hospitals, provides 60% of outpatient care, and 43% of hospitals with inpatients (10,11). The
31 Patient Pathway Analysis (PPA) study in 2017 revealed that 54% of the discovery and treatment
32 of TB has been carried out by government health facilities, 42% by the private sector, and
33 another 4%. The proportion of TB cases from government hospitals and government clinics
34 from the national target of 17% reached 16%, while from private hospitals the target of 23%
35 was reached 22%, and from Clinics and independent practice doctor of the target of 1%
36 achieved 2% (12). However, only 32% of cases are recorded, indicating that 68% of cases go
37 unreported. Most of these missing cases are believed to be in the private sector and go
38 unreported, even though some of them can receive both diagnosis and treatment at the same
39 time.
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3 The success of tuberculosis control in Indonesia can be described by three indicators.
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5 They are complete treatment rate (% complete rate), cure rate (% cure rate), and treatment
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7 success rate (% success rate). TB patients are therefore classified as cured, completed treatment,
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9 failed treatment, lost to follow-up, or died based on the outcome of their treatment. Lost to
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11 follow-up (LTFU) was defined as patients who received treatment for at least 4 weeks and the
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13 treatment was discontinued for more than eight consecutive weeks (13).
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17 Previous studies reported that the factors for increasing LTFU in TB patients were
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19 negative attitudes towards treatment, limited social support, dissatisfaction with health services,
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21 and limited economic status (14). A study in Namibia reported that male gender, age group 15-
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23 24 years, treatment service providers, TB intensive phase patients, and living in border/transit
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25 areas were factors for LTFU in TB patients (15). A meta-analysis study reported that the high
26
27 prevalence of LTFU in TB patients due to multidrug resistance, and the anatomic location of
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29 tuberculosis were significant factors (16). The significance of risk factors of LTFU (i.e. patient
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31 demographics, socioeconomic status, directly observed treatment, short-course (DOTS)
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33 programme, clinical covariates, TB treatment regimen and HIV co-infection) on LTFU has been
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35 contested across countries (15).
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40 One of the reasons for the development of acquired Drug Resistance Tuberculosis (DR-
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42 TB) is LTFU. Patients who are readmitted after LTFU are more likely to redevelop infectious
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44 active TB and are at higher risk of developing further drug resistant strains of tuberculosis
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46 (17,18). According to reports on the economic challenges of TB drug non-adherence, an
47
48 estimated 52 MDR-TB patients lost to follow-up resulted in 5 patients developing XDR-TB, 3
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50 newly infected MDR-TB and a new XDR-TB, and 3 deaths (16).
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53 LTFU can increase the risk of clinical deterioration, treatment failure, and further
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55 complications in tuberculosis patients. Patients who discontinue treatment too early are one of
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57 the leading causes of treatment failure (16). The dropout rate is critical because low LTFU as a
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3 result of improved TB management will reduce re-treatment case by 10-20% in the coming
4 years (7). This issue highlights the importance to study the predictors of LTFU during the PPM.
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10 **Methods**

11 *Study design and data source*

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14 This study is an analysis of secondary data from the Tuberculosis Information System (SITB)
15 through the TB03 form provided by the Ministry of Health. This system summarizes
16 tuberculosis patient data and treatment monitoring. Research data was collected from 2020 to
17 mid-2021. Respondents who were registered at SITB in 2020-2021 totaled 3400 respondents,
18 3434 respondents were examined for the final results of treatment, 384 were lost to follow-up,
19 the rest were patients who died who were not included in the analysis.
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28 *Data Management and Analysis*

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30 **Dependent variable:** Patients whose tuberculosis treatment status was lost to follow-up were
31 defined as discontinuing treatment for two or more consecutive months (8 weeks) for any reason
32 without medical consent (16).
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37 **Independent variables:** Independent variables that are fully recorded in SITB and can be
38 included in the final analysis include the variables of Year Diagnosed, Insurance Ownership,
39 Standard of Treatment, Gender, Occupational Status, Place of Residence, Close Contact
40 Examination, Referral Status, Type of Diagnosis Enforcement, Type of TB, Patient Referral
41 Status, Diabetes Mellitus Status, HIV Status, Drug Source.
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49 The year diagnosed is the year when the respondent first received a TB diagnosis through
50 molecular rapid tests, X-rays, and Mantoux which were classified into 2020 and 2021 (January
51 – July); Insurance ownership is classified into having insurance and not having insurance;
52 Standards of Treatment are respondents who are given treatment in accordance with the
53 National Guidelines for Medical Services for Tuberculosis Management ; Gender is classified
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3 into male and female; Employment status is classified into working and not working; Place of
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5 residence is categorized into Semarang City and Outside Semarang City; Close contact
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7 examination is classified into close contact examination or no close contact examination;
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9 Referral status is categorized into referral patients or patients who come alone to health services
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11 for TB tests; Methods of diagnosis are categorized into diagnosis of TB clinically or
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13 bacteriologically; The type of TB is classified into pulmonary TB or extrapulmonary
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15 tuberculosis; Patient status is categorized into whether the patient failed treatment or relapsed
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17 or new patient; Diabetes Mellitus status was grouped into positive TB patient Diabetes mellitus
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19 or negative TB patient diabetes mellitus; HIV status was categorized into TB patients who were
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21 HIV positive or TB patients who were HIV negative; and Sources of Drugs that are categorized
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23 into program drugs (free) or outside the program (own costs).
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28 *Statistical Analysis*

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30 The data is presented in frequency and percentage based on a LTFU status. Chi-square analysis
31
32 was performed to determine the relationship between the independent and dependent variables.
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34 P-value <0.05 was considered statistically significant. The independent variable, which has a
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36 p-value lower than 0.25, is included in the multivariable analysis. We analyzed the final model
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38 using Binary Regression Logistics Backward LR. All analyzes were performed by SPSS 22.0
39
40 (IBM Corporation, NY, USA).
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44 *Ethical approval*

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46 The Health Research Ethics Committee of Universitas Negeri Semarang has reviewed and
47
48 approved the protocol by issuing a letter numbered 095/KEPK/EC/2021.
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52 **Results**

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54 Health facilities in Semarang City consist of primary healthcare center, public and private
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56 hospitals, community pulmonary health center, as well as independent practice doctors and
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3 clinics which are reported through primary healthcare center and hospitals as referral health
4 facilities. All 37 primary healthcare center in Semarang (100%) participated in reporting and
5 recording TB cases. Likewise, 8 public hospitals and a primary healthcare center, all of them
6 (100%) participated in the reporting and recording TB cases. However, out of 21 private
7 hospitals in Semarang, only 90.5% private hospitals participated in reporting and recording TB
8 cases. Detailed data are presented in Table 1.

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17 Characteristics of respondents based on Tuberculosis Information System (SITB) data are
18 presented in Table 2. The average age of TB patients is 34.2 years old (SD: 28.9), with male
19 patients (53.9%) outnumbering female patients. Most of them live in Semarang (77.4%), while
20 the rest live in other neighboring cities. As many as 81.8% of pulmonary TB patients and their
21 sis were extra pulmonary TB patients. From the data analyzed, many TB patients have comorbid
22 diseases, 8.8% of TB patients had positive Diabetes Mellitus status while 1.5% of TB patients
23 had HIV positive.

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33 Patient characteristics, including age (p-value= <0.001), year of diagnosis (p-value
34 = 0.001 ; RR=0.730; 95% CI: 0.603- 0.883), gender (p-value=0.007; RR=1.305; 95% CI=1.076-
35 1.584), employment (p-value=0.013; RR=1.314; 95% CI=1.058-1.631), residence (p-
36 value= <0.001 ; RR =1.503, 95% CI=1.228-1.840), type of TB (p-value=0.013; RR=1.418; 95%
37 CI=1.072-1.874), Diabetes Mellitus (p-value= <0.001 ; RR = 1.852; 95% CI = 1.438-2.385), and
38 patient status (p-value=0.016; RR = 1.537; 95% CI = 1.018-2.321). These characteristics were
39 statistically associated with the incidence of LFTU during TB treatment. In addition, healthcare
40 and social security insurance ownership (p-value= <0.001 ; RR = 0.621; 95% CI = 0.495-0.779),
41 standard treatment (p-value= <0.001 ; RR=1.774; 95% CI=1.389-2.265), close contact
42 examination (p-value=0.018; RR=1.859; 95% CI=1.089-3.174), referral status (p-
43 value= <0.001 ; RR=0.574; 95% CI =0.432-0.764), diagnosis method (p-value=0.004;
44 RR=1.344; 95% CI= 1.100-1.643), drugs sources (p-value=0.045; RR:0.285; 95% CI=0.073-
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3 1.117) and had a positive significant relationship with the LTFU during TB treatment during
4 the PPM. Detailed data are presented in Table 3.
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7 The regression analysis was carried out by multivariate analysis (see Table 4). It revealed
8 4 key variables which became the predictive factors of lost to follow-up status during
9 tuberculosis treatment during the PPM. The variables are year of diagnose (AOR=1.541; p-
10 value=<0.001; 95% CI=1.228-1.934), referral status (AOR=1.562, p-value=0.007; 95%
11 CI=1.130-2.160), healthcare and social security insurance ownership (AOR=1.638; p-
12 value=<0.001; 95% CI=1.263-2.124, and drugs sources (AOR=4.667; p-value=0.035; 95%
13 CI=1.117-19489).
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26 Discussion

27 The national strategy of TB Control Program aims at providing universal access to
28 quality TB services through a systematic Find Cure Until Heal (TOSS) activity for all TB
29 patients supported by active participation of health care providers both in public and private
30 sectors (3,7,19). The PPM involves all health care facilities to expand TB patient services and
31 the continuity of a comprehensive TB control program. One of the objectives is to prevent
32 LTFU patients during TB treatment (7,19). Most health facilities in Semarang, both private and
33 public, have contributed to TB reporting. In practice, government health facilities (hospitals
34 and primary healthcare center) have reported more cases than private hospitals.
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46 The logistic regression analysis revealed three key factors that influenced the work of
47 LTFU in tuberculosis patients during the PPM period: the patient was referral, the patient did
48 not have any healthcare and social security insurance, and the medication received was not a
49 program drug. According to this study, the most significant factor influencing the incidence of
50 LTFU during the PPM period is patients who receive drug sources other than the program, with
51 4.6 times probability. These findings suggest that patients tend to use complementary medicine.
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3 Previous research has shown that in general, Asians use complementary medicine in addition
4 to conventional medicine (20). In addition, community's influence plays a strong role in TB
5 medication in Asia. Accessibility, tradition or belief, and feelings of dissatisfaction with
6 conventional drugs are all factors that encourage the use of alternative drugs. Another factor
7 that affects LTFU with 1.5 times probability is referral patients (21). Research in Pakistan
8 shows that patients who undergo treatment at referral health facilities and become referral
9 patients are more likely to experience LTFU before starting TB treatment (22). This is due to
10 the distance between the patient's residence and the facility. The greater the distance, the higher
11 the LTFU rate, particularly for patients living outside the city (23).

24 Because treatment is not cheap and takes a long time, health insurance is essential for
25 TB patients in Indonesia, who are mostly from lower-middle-class families. TB patients'
26 treatment costs more because they must pay for co-morbidity medication, transportation, and
27 accommodation (24). Furthermore, the indirect costs of TB treatment the patients have to
28 endure are reduced income or a lower proportion of household income, which can lead to deeper
29 poverty. According to previous research, the costs incurred when a person does not work while
30 on treatment account for 67% of the total costs incurred by TB patients (25).

40 The results of the study, which found that patients without health insurance had a 1.6
41 times greater likelihood of missing treatment, were relevant to previous studies because having
42 health insurance ensures that TB patients do not incur personal costs for care and treatment until
43 they are declared cured. The availability of health insurance is critical, particularly in cases of
44 TB with complications or additional conditions such as diabetes, hypertension, impaired kidney
45 function, pregnancy and lactation, or other diseases that necessitate additional examination and
46 treatment. Patients without health insurance must still pay for additional examinations,
47 hospitalization, or other drugs not covered by the government's TB program. Due to the high
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3 costs, TB patients, particularly those without health insurance, are more likely to be absent or
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5 to discontinue treatment (26).
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8 LTFU factors in TB patients should be better understood for a better understanding of
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10 treatment adherence challenges, especially during the PPM initiative. As a result, we
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12 recommend a qualitative study to assess other factors that increase the risk of LTFU that are
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14 reviewed in cross-sectoral services and support, particularly private health facilities in the PPM
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16 period, and how health workers treat LTFU patients. One limitation of this study is that we
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18 assessed LTFU using electronic records at the SITB rather than actively tracking patients.
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20 Furthermore, there is no access to a list of LTFU patients at facilities located outside of
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22 Semarang City, so it is possible that some TB patients have transferred treatment to locations
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24 outside of the city but are still classified as LTFU. However, as these patients represented only
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26 11.2% of all patients in this study, this factor is unlikely to have had much effect on the overall
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28 outcome. Another limitation is that because the data is secondary, we were unable to determine
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30 the exact factors for LTFU from the patient's perspective. Despite these limitations, this study
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32 extends our understanding of the factors that contribute to LTFU during TB treatment during
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34 the PPM initiative. The TB control program manager can use this information as key reference
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36 to optimize the implementation of PPM in the context of TB control.
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47
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53 **Competing Interests**

54
55 The authors declares that they have no competing interests with regards to authorship and/or
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57 publication of this article.
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Author's Contribution

All authors contributed to the study conception and design. SRR: conceptualization, methodology, writing review and editing draft; MSS: conceptualization, project administration writing review and editing draft; MZS: data curation, formal analysis, methodology, writing original draft; MA: methodology and writing original draft; FI: data curation and formal analysis; MS: project administration and supervision; DM: conceptualization and formal analysis; BDS: methodology and project administration; SD: data curation and formal analysis; ANM: conceptualization, data curation, formal analysis, methodology, review & editing; RA: formal analysis and project administration; MDA: conceptualization, project administration and resources; NW: data curation, writing review & editing; I: formal analysis, review & editing; ADW: investigation and project administration; AKL: formal analysis and investigation; ZM: formal analysis, methodology, writing review & editing. All authors read and approved the final manuscript.

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For Review Only

Table 1. Characteristics of health facilities at the research site

Type of Health Facilities	Number of health facilities reporting TB	Total of health facilities	%
Primary Healthcare Center	37	37	100
Public Hospitals	8	8	100
Private Hospitals	19	21	90.5
Community Pulmonary Health Center	1	1	100
Average			97.6

For Review Only

Table 2. Characteristics of Tuberculosis patients in Semarang City based on data from Tuberculosis Information System (SITB) (N=3434)

Characteristic	Frequency (n)	Percentage (%)
Age (mean; SD)	34.2; 28.9	
Year of Diagnosis		
2020	2282	66.5
2021	1152	33.5
Sex		
Male	1851	53.9
Female	1583	46.1
Employment Status		
Employed	2348	68.4
Unemployed	1086	31.6
Residence Status		
Out of town	775	22.6
In the town	2659	77.4
TB Types		
Pulmonary TB	2810	81.8
Pulmonary Extract TB	624	18.2
Diabetes Mellitus Status		
Positive	301	8.8
Negative	3133	91.2
HIV Status		
Positive	51	1.5
Negative	3383	98.5
Patient Status		
Treatment failure	120	3.5
Relapse	49	1.4
New Patients	3265	95.1

Table 3. Cross-tabulation predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	Final Result of Treatment				RR	95% CI	p-Value
	LTFU		Recovery				
	n	%	n	%			
Age (mean; SD)	384	11.2	3050	88.8	-	6.405-10.825	<0.001
Year of Diagnosis							
2020	227	9.9	2055	90.1	0.730	0.603-0.883	0.001
2021	157	13.6	995	86.4			
Healthcare and Social Security Agency ownership							
Do not have	88	7.9	1024	92.1	0.621	0.495-0.779	<0.001
Have	296	12.7	2026	87.3			
Treatment Standard							
Non-standard	64	18.4	284	81.6	1.774	1.389-2.265	<0.001
Standard	320	10.4	2766	89.6			
Sex							
Male	232	12.5	1619	87.5	1.305	1.076-1.584	0.007
Female	152	9.6	1431	90.4			
Employment Status							
Employed	284	12.1	2064	87.9	1.314	1.058-1.631	0.013
Unemployed	100	9.2	986	90.8			
Residence							
Out of town	117	15.1	658	84.9	1.503	1.228-1.840	<0.001
In the town	267	10.0	2392	90.0			
Close Contact Examination							
No	371	11.5	2853	88.5	1.859	1.089-3.174	0.018
Yes	13	6.2	197	93.8			
Referral Status							
Referral	50	7.0	660	93.0	0.574	0.432-0.764	<0.001
Non-referral	334	12.3	2390	87.7			
Diagnose Method							
Clinical	255	12.5	1789	87.5	1.344	1.100-1.643	0.004
Bacteriological	129	9.3	1261	90.7			
TB Types							
Pulmonary TB	332	11.8	2478	88.2	1.418	1.072-1.874	0.013
Pulmonary Extract TB	52	8.3	572	91.7			
Patient Status							
Treatment failure	20	16.7	100	83.3	ref.	ref.	0.016
Relapse	10	20.4	39	79.6	0.817	0.413-1.616	
New Patients	354	10.8	2911	89.2	1.537	1.018-2.321	
Diabetes Mellitus Status							
Positive	58	19.3	243	80.7	1.852	1.438-2.385	<0.001
Negative	326	10.4	2807	89.6			
HIV Status							
Positive	9	17.6	42	82.4	1.592	0.873-2.902	0.14
Negative	375	11.1	3008	88.9			
Drug Source							
Apart from program	2	3.2	60	96.8	0.285	0.073-1.117	0.045
From program	382	11.3	2990	88.7			

*P-value<0.05 = significant

Table 4. Logistic Regression predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

	<i>P</i> -Value	Adjusted OR	95%CI
Year of Diagnosis	<0.001	1.541	1.228-1.934
Referral Status	0.007	1.562	1.130-2.160
Healthcare and Social Security	<0.001	1.638	1.263-2.124
Agency Ownership			
Drug Source	0.035	4.667	1.117-19.489

For Review Only

ORIGINAL ARTICLE**Lost to Follow-Up among Tuberculosis Patients during the Public-Private Mix Era in Rural Area of Indonesia**

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ABSTRACT

BACKGROUND: Indonesia's national Tuberculosis (TB) strategy is public-private mix (PPM). The PPM aims to treat patients who have lost sight during TB treatment as these patients are TB carriers and at risk of transmitting TB. The purpose of this study was to identify predictive factors for loss to follow-up (LFTU) among TB patients receiving treatment when the PPM was at place in Indonesia.

METHODS: The design of this study was a retrospective cohort study. The data used in this study was sourced from the Tuberculosis Information System (SITB) of Semarang which was recorded routinely during 2020-2021. Univariate analysis, crosstabulation, and logistic regression were performed on 3434 TB patients meeting the minimum variables.

RESULTS: The participation of health facilities in reporting TB during the PPM era in Semarang reached 97.6% consisting of 37 primary healthcare center (100%), 8 public hospitals (100%), 19 private hospitals (90.5%), and a community-based pulmonary health center (100%). The regression analysis reveal that the predictive factors of LFTU-TB during the PPM are the year of diagnosis (AOR=1.541; p -value= <0.001 ; 95% CI=1.228-1.934), referral status (AOR=1.562, p -value=0.007; 95% CI=1.130-2160), healthcare and social security insurance ownership (AOR=1.638; p -value= <0.001 ; 95% CI=1.263-2.124), drugs source (AOR=4.667; p -value=0.035; 95% CI=1.117-19.489).

CONCLUSIONS: The PPM strategy in dealing with LFTU patients should focus on TB patients without Healthcare and Social Security Insurance and who receive TB treatment rather than program drugs.

KEYWORDS: Health Facilities, Lost to Follow-Up, Tuberculosis, Indonesia

INTRODUCTION

Tuberculosis (TB) is an infectious disease that remains a major health problem worldwide. In 2019, the number of people diagnosed and confirmed TB cases reached 7.1 million

globally (1). World Health Organization (WHO) estimates that there is a 2.9-million gap between the number of diagnosed TB cases and the number of notified cases due to the high unreported cases. One country that accounts for more than half of the global gap is Indonesia (10%) (2). The National TB strategy implemented in Indonesia and several other countries such as in Ethiopia is to increase case finding as the main focus of TB control (3-5).

WHO global policy for TB control is to involve all service providers through a Public-Private Mix (PPM) approach (1,6). The goal of PPM is to improve case detection and treatment success that contributes to missing cases (7,8). The target providers are not only private and corporate sector (hospitals or institutions, private practitioners), and voluntary sector (non-government organization or community-based organizations), but also public sector itself (many types of public providers such as general and specialty hospitals, teaching hospitals, prisons, military-owned providers and others who have not joined the program (8,9). The case network is one of the PPM network's principles, namely the continuity of treatment of TB patients from referrals/transfers and the tracking of TB patients who are lost to follow-up (10).

This policy has also been adopted by the Government of Indonesia. Research evidence in India and Myanmar shows that PPM strengthens TB care and control (11). Research in Pakistan shows that Among the PPM approaches, general practitioners and non-governmental organization facilities achieve 94-95% treatment success; private hospitals achieved 82% success (12)

The PPM approach is to ensure equitable, quality, and sustainable access to TB services for those affected by TB (universal access) in ensuring TB patients' recovery. However, within the Indonesian context, private sector involvement remains low (9). According to Indonesia National Development Planning Agency, the private sector manages more than 50% of hospitals, provides 60% of outpatient care, and 43% of hospitals with inpatients (9,13). The Patient Pathway Analysis (PPA) study in 2017 revealed that 54% of the discovery and treatment of TB has been carried out by government health facilities, 42% by the private

sector, and another 4%. The proportion of TB cases from government hospitals and government clinics from the national target of 17% reached 16%, while from private hospitals the target of 23% was reached 22%, and from Clinics and independent practice doctor of the target of 1% achieved 2% (14). However, only 32% of cases are recorded, indicating that 68% of cases go unreported. Most of these missing cases are believed to be in the private sector and go unreported, even though some of them can receive both diagnosis and treatment at the same time.

The success of tuberculosis control in Indonesia can be described by three indicators. They are complete treatment rate (% complete rate), cure rate (% cure rate), and treatment success rate (% success rate). TB patients are therefore classified as cured, completed treatment, failed treatment, lost to follow-up, or died based on the outcome of their treatment. Lost to follow-up (LTFU) was defined as patients who received treatment for at least 4 weeks and the treatment was discontinued for more than eight consecutive weeks (15).

Previous studies reported that the factors for increasing LTFU in TB patients were negative attitudes towards treatment, limited social support, dissatisfaction with health services, and limited economic status (16). A study in Namibia reported that male gender, age group 15-24 years, treatment service providers, TB intensive phase patients, and living in border/transit areas were factors for LTFU in TB patients (17). A meta-analysis study reported that the high prevalence of LTFU in TB patients due to multidrug resistance, and the anatomic location of tuberculosis were significant factors (18). The significance of risk factors of LTFU (i.e. patient demographics, socioeconomic status, directly observed treatment, short-course (DOTS) programme, clinical covariates, TB treatment regimen and HIV co-infection) on LTFU has been contested across countries (17). One of the reasons for the development of acquired Drug Resistance Tuberculosis (DR-TB) is LTFU. Patients who are readmitted after LTFU are more likely to redevelop infectious active TB and are at higher risk of developing further drug resistant strains of tuberculosis

(19,20). According to reports on the economic challenges of TB drug non-adherence, an estimated 52 MDR-TB patients lost to follow-up resulted in 5 patients developing XDR-TB, 3 newly infected MDR-TB and a new XDR-TB, and 3 deaths (18).

LTFU can increase the risk of clinical deterioration, treatment failure, and further complications in tuberculosis patients. Patients who discontinue treatment too early are one of the leading causes of treatment failure (18). The dropout rate is critical because low LTFU as a result of improved TB management will reduce re-treatment case by 10-20% in the coming years (10). This issue highlights the importance to study the predictors of LTFU during the PPM.

METHODS

Study design and data source: This study is an analysis of secondary data from the Tuberculosis Information System (SITB) through the TB03 form provided by the Ministry of Health. This system summarizes tuberculosis patient data and treatment monitoring. Research data was collected from 2020 to mid-2021. Respondents who were registered at SITB in 2020-2021 totaled 3400 respondents, 3434 respondents were examined for the final results of treatment, 384 were lost to follow-up, the rest were patients who died who were not included in the analysis.

Dependent variable: Patients whose tuberculosis treatment status was lost to follow-up were defined as discontinuing treatment for two or more consecutive months (8 weeks) for any reason without medical consent (18).

Independent variables: Independent variables that are fully recorded in SITB and can be included in the final analysis include the variables of Year Diagnosed, Insurance Ownership, Standard of Treatment, Gender, Occupational Status, Place of Residence, Close Contact Examination, Referral Status, Type of Diagnosis Enforcement, Type of TB, Patient Referral Status, Diabetes Mellitus Status, HIV Status, Drug Source.

The year diagnosed is the year when the respondent first received a TB diagnosis through molecular rapid tests, X-rays, and Mantoux which were classified into 2020 and 2021 (January – July); Insurance ownership is

classified into having insurance and not having insurance; Standards of Treatment are respondents who are given treatment in accordance with the National Guidelines for Medical Services for Tuberculosis Management; Gender is classified into male and female; Employment status is classified into working and not working; Place of residence is categorized into Semarang City and Outside Semarang City; Close contact examination is classified into close contact examination or no close contact examination; Referral status is categorized into referral patients or patients who come alone to health services for TB tests; Methods of diagnosis are categorized into diagnosis of TB clinically or bacteriologically; The type of TB is classified into pulmonary TB or extrapulmonary tuberculosis; Patient status is categorized into whether the patient failed treatment or relapsed or new patient; Diabetes Mellitus status was grouped into positive TB patient Diabetes mellitus or negative TB patient diabetes mellitus; HIV status was categorized into TB patients who were HIV positive or TB patients who were HIV negative; and Sources of Drugs that are categorized into program drugs (free) or outside the program (own costs).

Statistical analysis: The data is presented in frequency and percentage based on a LTFU status. Chi-square analysis was performed to determine the relationship between the independent and dependent variables. P-value <0.05 was considered statistically significant. The independent variable, which has a p-value lower than 0.25, is included in the multivariable analysis. We analyzed the final model using Binary Regression Logistics Backward LR. All analyzes were performed by SPSS 22.0 (IBM Corporation, NY, USA).

Ethical approval: The Health Research Ethics Committee of Universitas Negeri Semarang has reviewed and approved the protocol by issuing a letter numbered 095/KEPK/EC/2021.

RESULTS

Health facilities in Semarang City consist of primary healthcare center, public and private hospitals, community pulmonary health center, as well as independent practice doctors and clinics which are reported through primary

healthcare center and hospitals as referral health facilities. All 37 primary healthcare center in Semarang (100%) participated in reporting and recording TB cases. Likewise, 8 public hospitals and a primary healthcare center, all of them

(100%) participated in the reporting and recording TB cases. However, out of 21 private hospitals in Semarang, only 90.5% private hospitals participated in reporting and recording TB cases (Fig. 1).

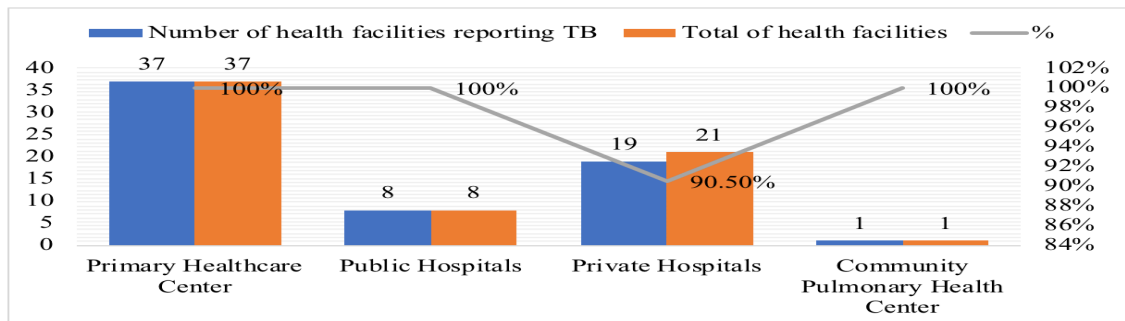


Figure 1: Characteristics of health facilities at the research site

Characteristics of respondents based on Tuberculosis Information System (SITB) data are presented in Table 1. The average age of TB patients is 34.2 years old (SD: 28.9), with male patients (53.9%) outnumbering female patients. Most of them live in Semarang (77.4%), while the rest live in other neighboring cities. As many as 81.8% of pulmonary TB patients and their sis were extra pulmonary TB patients. From the data analyzed, many TB patients have comorbid diseases, 8.8% of TB patients had positive Diabetes Mellitus status while 1.5% of TB patients had HIV positive.

Patient characteristics, including age (p -value= <0.001), year of diagnosis (p -value =0.001; RR=0.730; 95% CI: 0.603- 0.883), gender (p -value=0.007; RR=1.305; 95% CI=1.076-1.584), employment (p -value=0.013; RR=1.314; 95% CI=1.058-1.631), residence (p -value= <0.001 ; RR =1.503, 95% CI=1.228-1.840), type of TB (p -value=0.013; RR=1.418; 95% CI=1.072-1.874), Diabetes Mellitus (p -value= <0.001 ; RR = 1.852; 95% CI = 1.438-2.385), and patient status (p -value=0.016; RR = 1.537; 95% CI = 1.018-2.321). These characteristics were statistically associated with the incidence of LFTU during TB treatment. In addition, healthcare and social security insurance ownership (p -value= <0.001 ; RR 0.621; 95% CI = 0.495-0.779), standard treatment (p -value= <0.001 ; RR=1.774; 95% CI=1.389-2.265), close contact examination (p -value=0.018; RR=1.859; 95% CI=1.089-3.174), referral status (p -value= <0.001 ; RR=0.574; 95% CI =0.432-0.764), diagnosis method (p -value=0.004; RR=1.344; 95% CI= 1.100-1.643), drugs sources (p -value=0.045; RR:0.285; 95% CI=0.073-1.117)

and had a positive significant relationship with the LFTU during TB treatment during the PPM (Table 2).

Table 1: Characteristics of Tuberculosis patients in Semarang City based on data from Tuberculosis Information System (SITB) (N=3434).

Characteristic	Frequency (n)	Percent
Age (mean; SD)	34.2; 28.9	
Year of Diagnosis		
2020	2282	66.5
2021	1152	33.5
Sex		
Male	1851	53.9
Female	1583	46.1
Employment Status		
Employed	2348	68.4
Unemployed	1086	31.6
Residence Status		
Out of town	775	22.6
In the town	2659	77.4
TB Types		
Pulmonary TB	2810	81.8
Pulmonary Extract TB	624	18.2
Diabetes Mellitus Status		
Positive	301	8.8
Negative	3133	91.2
HIV Status		
Positive	51	1.5
Negative	3383	98.5
Patient Status		
Treatment failure	120	3.5
Relapse	49	1.4
New Patients	3265	95.1

Table 2: Cross-tabulation predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era

Variable	Final Result of Treatment				RR	95% CI	p-Value
	LTFU		Recovery				
	n	%	n	%			
Age (mean; SD)	384	11.2	3050	88.8	-	6.405-10.825	<0.001
Year of Diagnosis							
2020	227	9.9	2055	90.1	0.730	0.603-0.883	0.001
2021	157	13.6	995	86.4			
Healthcare and Social Security							
Agency ownership							
Do not have	88	7.9	1024	92.1	0.621	0.495-0.779	<0.001
Have	296	12.7	2026	87.3			
Treatment Standard							
Non-standard	64	18.4	284	81.6	1.774	1.389-2.265	<0.001
Standard	320	10.4	2766	89.6			
Sex							
Male	232	12.5	1619	87.5	1.305	1.076-1.584	0.007
Female	152	9.6	1431	90.4			
Employment Status							
Employed	284	12.1	2064	87.9	1.314	1.058-1.631	0.013
Unemployed	100	9.2	986	90.8			
Residence							
Out of town	117	15.1	658	84.9	1.503	1.228-1.840	<0.001
In the town	267	10.0	2392	90.0			
Close Contact Examination							
No	371	11.5	2853	88.5	1.859	1.089-3.174	0.018
Yes	13	6.2	197	93.8			
Referral Status							
Referral	50	7.0	660	93.0	0.574	0.432-0.764	<0.001
Non-referral	334	12.3	2390	87.7			
Diagnose Method							
Clinical	255	12.5	1789	87.5	1.344	1.100-1.643	0.004
Bacteriological	129	9.3	1261	90.7			
TB Types							
Pulmonary TB	332	11.8	2478	88.2	1.418	1.072-1.874	0.013
Pulmonary Extract TB	52	8.3	572	91.7			
Patient Status							
Treatment failure	20	16.7	100	83.3	ref.	ref.	0.016
Relapse	10	20.4	39	79.6	0.817	0.413-1.616	
New Patients	354	10.8	2911	89.2	1.537	1.018-2.321	
Diabetes Mellitus Status							
Positive	58	19.3	243	80.7	1.852	1.438-2.385	<0.001
Negative	326	10.4	2807	89.6			
HIV Status							
Positive	9	17.6	42	82.4	1.592	0.873-2.902	0.14
Negative	375	11.1	3008	88.9			
Drug Source							
Apart from program	2	3.2	60	96.8	0.285	0.073-1.117	0.045
From program	382	11.3	2990	88.7			

*P-value<0.05 = significant

The regression analysis was carried out by multivariate analysis (see Table 3). It revealed 4 key variables which became the predictive factors of lost to follow-up status during tuberculosis treatment during the PPM. The variables are year of diagnose (AOR=1.541; p-value=<0.001; 95% CI=1.228-1.934), referral

status (AOR=1.562, p-value=0.007; 95% CI=1.130-2.160), healthcare and social security insurance ownership (AOR=1.638; p-value=<0.001; 95% CI=1.263-2.124, and drugs sources (AOR=4.667; p-value=0.035; 95% CI=1.117-19489).

Table 3: Logistic Regression predictive factors of lost to follow-up status during tuberculosis treatment in public-private mix era.

Variable	P-Value	Adjusted OR	95%CI
Year of Diagnosis	<0.001	1.541	1.228-1.934
Referral Status	0.007	1.562	1.130-2.160
Healthcare and Social Security Agency Ownership	<0.001	1.638	1.263-2.124
Drug Source	0.035	4.667	1.117-19.489

*P-value<0.05 = significant

DISCUSSION

The national strategy of TB Control Program aims at providing universal access to quality TB services through a systematic Find Cure Until Heal (TOSS) activity for all TB patients supported by active participation of health care providers both in public and private sectors (6,10,21). The PPM involves all health care facilities to expand TB patient services and the continuity of a comprehensive TB control program. One of the objectives is to prevent LTFU patients during TB treatment (10,21). Most health facilities in Semarang, both private and public, have contributed to TB reporting. This contribution was supported by the fact that TB patients have good knowledge on signs and symptoms of TB, transmission of TB and healthcare seeking behavior of TB (22). In practice, government health facilities (hospitals and primary healthcare center) have reported more cases than private hospitals.

The logistic regression analysis revealed three key factors that influenced the work of LTFU in tuberculosis patients during the PPM period: the patient was referral, the patient did not have any healthcare and social security insurance, and the medication received was not a program drug. According to this study, the most significant factor influencing the incidence of LTFU during the PPM period is patients who receive drug sources other than the program, with 4.6 times probability. These findings

suggest that patients tend to use complementary medicine. Previous research has shown that in general, Asians use complementary medicine in addition to conventional medicine (23). In addition, community's influence plays a strong role in TB medication in Asia. Accessibility, tradition or belief, and feelings of dissatisfaction with conventional drugs are all factors that encourage the use of alternative drugs. Another factor that affects LTFU with 1.5 times probability is referral patients (24). Research in Pakistan shows that patients who undergo treatment at referral health facilities and become referral patients are more likely to experience LTFU before starting TB treatment (25). This is due to the distance between the patient's residence and the facility. The greater the distance, the higher the LTFU rate, particularly for patients living outside the city (26).

Because treatment is not cheap and takes a long time, health insurance is essential for TB patients in Indonesia, who are mostly from lower-middle-class families. TB patients' treatment costs more because they must pay for co-morbidity medication, transportation, and accommodation (27). Furthermore, the indirect costs of TB treatment the patients have to endure are reduced income or a lower proportion of household income, which can lead to deeper poverty. According to previous research, the costs incurred when a person does not work while on treatment account for 67% of the total costs incurred by TB patients (28).

The results of the study, which found that patients without health insurance had a 1.6 times greater likelihood of missing treatment, were relevant to previous studies because having health insurance ensures that TB patients do not incur personal costs for care and treatment until they are declared cured. The availability of health insurance is critical, particularly in cases of TB with complications or additional conditions such as diabetes, hypertension, impaired kidney function, pregnancy and lactation, or other diseases that necessitate additional examination and treatment. Patients without health insurance must still pay for additional examinations, hospitalization, or other drugs not covered by the government's TB program. Due to the high costs, TB patients, particularly those without health insurance, are more likely to be absent or to discontinue treatment (29).

LTFU factors in TB patients should be better understood for a better understanding of treatment adherence challenges, especially during the PPM initiative. As a result, we recommend a qualitative study to assess other factors that increase the risk of LTFU that are reviewed in cross-sectoral services and support, particularly private health facilities in the PPM period, and how health workers treat LTFU patients. One limitation of this study is that we assessed LTFU using electronic records at the SITB rather than actively tracking patients. Furthermore, there is no access to a list of LTFU patients at facilities located outside of Semarang City, so it is possible that some TB patients have transferred treatment to locations outside of the city but are still classified as LTFU. However, as these patients represented only 11.2% of all patients in this study, this factor is unlikely to have had much effect on the overall outcome. Another limitation is that because the data is secondary, we were unable to determine the exact factors for LTFU from the patient's perspective. Despite these limitations, this study extends our understanding of the factors that contribute to LTFU during TB treatment during the PPM initiative. The TB control program manager can use this information as key reference to optimize the implementation of PPM in the context of TB control.

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