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Meta-Analysis

Urine Test Accuracy of Lipoarabinomannan in Diagnosing Pulmonary Tuberculosis in Adults: Meta-Analysis

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ABSTRACT

Background: Mycobacterium tuberculosis (Mt) requires non-sputum-based screening that can identify it with high sensitivity and specificity. Lipoarabinomannan (LAM) is a diagnosis of active tuberculosis (TB) in samples such as urine, both by complex laboratory-based testing and in simple treatment tools. The purpose of this study was to determine the accuracy of the Lipoarabinomannan urine test in diagnosing TB in adults.
Subjects and Method: This study is a meta-analysis study with PICO covering, population= adult age with suspected tuberculosis (TB). Intervention= lipoarabinomannan urine test. Comparison: no lipoarabinomannan urine test was performed. Outcome: sensitivity and specificity. Using the PRISMA flowchart guidelines. The articles used were conducted between 2012-2021 from the PubMed, Google Scholar, MedLine, and Science Direct databases. The keywords used in the article search were "Lipoarabinomannan" AND "LAM" OR "Adult" AND "Patient" OR "Diagnosis" OR "Pulmonary tuberculosis". Based on the database, there were 9 articles that matched the inclusion criteria. Data analysis using the RevMan 5.3 application.
Results: A total of 9 cohort studies with a total of 3,069 patients from South Africa (Cape Town, KwaZulu-Natal, Zimbabwe), East Africa (Kenya, Malawi, Tanzania, Uganda, Zambia), West Africa (Ghana) and South America (Peru) were selected for the study. systematic review and meta-analysis. A meta-analysis of 9 cohort studies showed that the lipoarabinomannan urine test had 2.89 times the accuracy or sensitivity in diagnosing TB compared to no lipoarabinomannan urine test (aOR= 2.89; 95% CI= 2.30 to 3.63; p= 0.160), but was not statistically significant.
Conclusion: The lipoarabinomannan urine test improves accuracy in diagnosing pulmonary tuberculosis in adults but is not statistically significant.

Keywords: lipoarabinomannan, LAM, adult, patient, diagnosis, pulmonary tuberculosis.

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BACKGROUND

Tuberculosis (TB) is a global health problem which according to a report by the World Health Organization (WHO) is the most severe infectious disease. It is estimated that around 23% of the world's population is infected with Mycobacterium tuberculosis (Mt) (Correia-Neves et al., 2019). TB occupies the tenth largest cause of death globally (Izudi et al., 2019) with at least 10 million people suffering from TB in 2019 and more than 1.2 million total deaths from the disease (Jakhar et al., 2020). In addition, TB is also the first cause of death

for people with Human Immunodeficiency Virus (HIV) (Izudi et al., 2019).

The high incidence and death rate due to TB is a serious problem that must be considered because of delays in diagnostic facilities, disease transmission can increase health care costs and increase mortality because it causes greater lung damage resulting in chronic disability. There are several TB diagnoses that have become the mainstay since 1882, namely the TB skin test (TST), sputum culture and radiology examinations. Sputum microscopy has a high specificity in the setting of a high prevalence of TB. However, the sensitivity for diagnosing pulmonary tuberculosis using the direct sputum smear method ranges from 40% to 60%. Sputum culture has low sensitivity for extrapulmonary TB (Agha et al., 2013).

Symptom-based screening has proven unreliable because there are no asymptomatic TB infected people, this screening identifies many people who need additional testing (Drain et al., 2015). A new method should ideally be non-sputum based and be able to identify Mt with high sensitivity and specificity regardless of age, nutritional status, or HIV status (Nkereuwem et al., 2021).

Lipoarabinomannan (LAM) is a lipopolysaccharide in the Mt cell wall that is released from metabolically active or destructive organisms and excreted in the urine. A new lateral flow assay for detecting LAM in urine requires no laboratory equipment or reagents, returns test results within 25 minutes, and can be performed at the point of clinical care (Drain et al., 2015). The test for urinary LAM is potentially useful in diagnostic algorithms as a rule test for HIV-associated TB and the evidence was assessed by WHO in 2014. Detection of LAM mycobacterial cell wall antigen in urine can be used to diagnose TB. However, it is not known whether the amount of LAM present in the urine provides additional prognostic information (Kerkhoff et al., 2014).

LAM detection assays, namely enzyme-linked immunosorbent assay (ELISA-Clearview TB-ELISA, Alere Inc, Waltham, MA, USA), simple point of care test (lateral flow, definitive TB-LAM assay (Alere Inc) and FujiLAM assay derived from Japan. LAM Elisa can be used for quantitative readings expressed as optical density (OD) at 450 mm. LAM ELISA assessment shows a very strong correlation between OD and pure LAM concentration. However, little is known whether quantification of LAM provides useful additional information clinically (Kerkhoff et al., 2014).

Based on this background, a comprehensive review of various primary studies on the accuracy of the lipoarabinomannan urine test is needed in diagnosing pulmonary TB in adults. This study aimed to assess the accuracy of the lipoarabinomannan urine test in diagnosing pulmonary TB in adults, with a meta-analysis of the main study conducted by the previous authors.

SUBJECTS AND METHOD

1. Study Design

This research was conducted using a meta-analysis research design with PRISMA flowchart guidelines. Research article searches were conducted using several databases: PubMed, Google Scholar, MedLine and Science Direct between 2012 and 2021. The keywords used in the article search were “Lipoarabinanan Test” AND “LAM” OR “Adult” AND “Patien” OR “Diagnosis” OR “Pulmonary tuberculosis”.

2. Inclusion Criteria

The inclusion criteria in this study were: full text articles using a cohort study design.

The study subjects were adults aged eighteen years or older with suspected TB, a study of the diagnostic value of the lipoarabinomannan urine test for TB which was designed as a diagnostic accuracy study, a study that provided reliable data. sufficient (true positive/negative, false positive/ negative) to calculate sensitivity and specificity pooled, multivariate analysis with adjusted odds ratio to estimate effect size.

3. Exclusion Criteria

Exclusion criteria in this study were that the study did not provide available data to calculate effect sizes or was missing other important information: reviews, abstracts, unpublished data or overlapping studies.

4. Definition Operational of Variable

The search for articles was carried out by considering the eligibility criteria determined using the PICO model. Population: adults with suspected Tuberculosis (TB). Intervention: lipoarabinomannan urine test. Comparison: no lipoarabinomannan urine test was performed. Outome: sensitivity and specificity.

The urine lipoarabinomannan test is a component of the mycobacterial cell wall that has been assessed as a potential biomarker for the diagnosis of active TB in samples such as urine, sputum and serum, both by complex laboratory-based assays and in simple treatment tools (Sossen and Bielawski, 2021).

Sensitivity is the ability of the test to show which individuals are sick from the entire population who are really sick.

Specificity is the accuracy of the test to show which individuals do not suffer from pain from those who are really sick (Siswosudarmo, 2017).

5. Study Instruments

The research was guided using the PRISMA flow chart and quality assessment using the Critical Appraisal Skills Program (CASP, 2018).

6. Data Analysis

The data in this study were analyzed using the Review Manager application (RevMan 5.3), to calculate the effect size and heterogeneity of the study. The results of data processing are presented in the form of forest plots and funnel plots. The fixed effects model is used for homogeneous data, while the random effects model is used for heterogeneity between studies.

RESULTS

The article search process is carried out through several journal databases, includeing: PubMed, Google Scholar, MedLine and Science Direct. The related article review process is shown in the PRISMA flow chart in figure 1. Research related to the Lipoarabinomannan Urine Test for the diagnosis of Pulmonary Tuberculosis in Adults consisted of 166 articles from the initial search process yielding 80 articles, after the deletion process of published articles was considered eligible. of which meet the requirements for further full-text review. A total of 9 articles that met the quality assessment were included in the quantitative synthesis using meta-analysis.

It can be seen in Figure 2. that the research articles come from two continents, namely Africa and America. Table 1, the researchers conducted an assessment of the quality of the study. Table 2 shows that 9 articles from cohort studies reported diagnostic value regarding the sensitivity and specificity of the LAM Test for the diagnosis of Tuberculosis in Adults.

Based on the results of the forest plot in Figure 3, it is shown that in the cohort study, the LAM urine test increased accuracy by 2.89 times compared to not performing the LAM urine test (aOR= 2.89; 95% CI= 2.30 to 3.63; p = 0.160) and was not statistically significant. The heterogeneity of the data shows I2 = 33% so that

the distribution of the data is declared homogeneous (fix effect model).

The funnel plot in the cohort study showed a publication bias characterized by an asymmetric distribution between the right and left plots with the estimated effect being overestimated. The plot on the right is 3 plots with a standard error (SE) between 0 and 1, and the plot on the left is 5 with a standard error (SE) between 0 and 2, and 1 plot touches the vertical line.

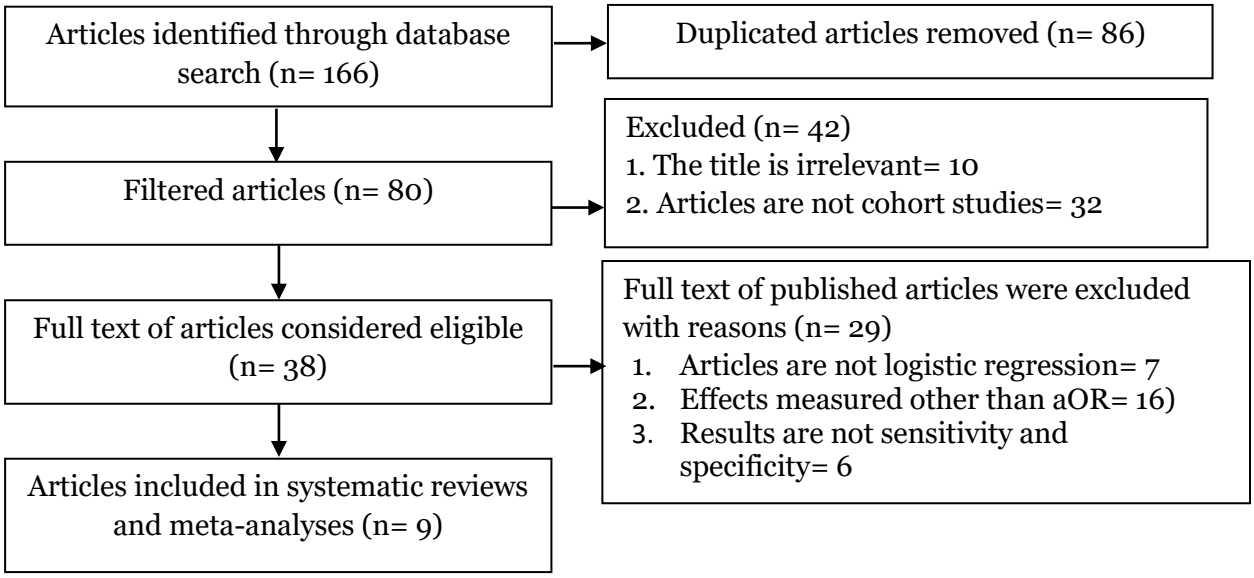

Figure 1 PRISMA Flowchart

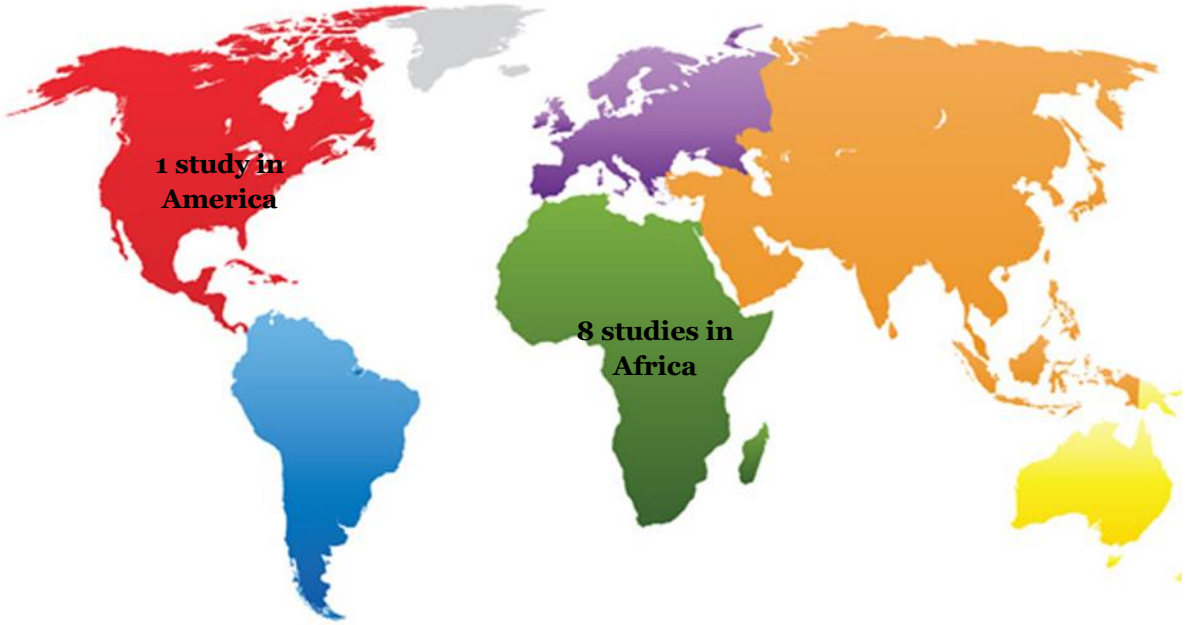

Figure 2. Map of Study Area

Table 1. Assessment of Publication Quality with Critical Appraisal Skills Cohort Study Design Program (CASP, 2018)

No	Indicator	Journal (Author and Year)				
		Kerkhoff et al. (2014)	Huerga et al. (2017)	Lawn et al. (2017)	Manabe et al. (2014)	Bjerrum et al. (2020)
1	Does the cohort study clearly address the clinical problem?	2	2	2	2	2
2	Were the co-hots (subjects in the exposed and unexposed groups) selected in the right way?	2	2	2	2	2
3	Is exposure measured accurately (correctly) to prevent/ minimize bias?	2	2	2	2	2
4	Are outcomes measured accurately (correctly) to minimize bias?	2	2	2	2	2
5	a. Did the researcher identify all the important confounding factors?	2	2	2	2	2
6	b. Has the researcher controlled for significant confounding factors in the design and/or analysis phase of the data?	2	2	0	2	0
7	a. Did the research subject complete the full time of the study?	2	2	2	2	2
8	b. Were the research subjects followed (follow-up) for a long time?	2	2	2	2	2
9	What are the results of this study?	2	2	2	2	2
10	How precise are the results?	2	2	2	2	2
11	Are the results reliable?	2	2	2	2	2
	Total	**26**	**26**	**24**	**26**	**24**

Note:
2: Yes; 1: Can't tell; 0: No

Table 2. Cont.

No	Indicator	Jurnal (Penulis dan Tahun)			
		De-Vasconcellos et al. (2021)	Paris et al. (2017)	Gupta-Wright et al. (2019)	Huerga et al. (2021)
1	Does the cohort study clearly address the clinical problem?	2	2	2	2
2	Were the co-hots (subjects in the exposed and unexposed groups) selected in the right way?	2	2	2	2
3	Is exposure measured accurately (correctly) to prevent/minimize bias?	2	2	2	2
4	Are outcomes measured accurately (correctly) to minimize bias?	2	2	2	2
5	a. Did the researcher identify all the important confounding factors?	2	2	2	2
6	b. Has the researcher controlled for significant confounding factors in the design and/or analysis phase of the data?	0	0	2	2
7	a. Did the research subject complete the full time of the study?	2	2	2	2
8	b. Were the research subjects followed (follow-up) for a long time?	2	2	2	2
9	What are the results of this study?	2	2	2	2
10	How precise are the results?	2	2	2	2
11	Are the results reliable?	2	2	2	2
	Total	**24**	**24**	**26**	**26**

Note: 2= Yes; 1= Can't tell; 0= No

Table 3. Description of the primary studies included in the meta-analysis dasar base study

Author (Year)	Country	Study Design	Sample		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aOR 95%CI
			Total	LAM					
Paris et al. (2017)	Peru	Prospective Cohort	101	48	HIV negative patient with TB	TB-LAM urin urine test	No urine test LAM	Sensitivity and specificity	0.26 (0.01 to 7.2)
Kerkhoff et al. (2014)	Cape Town	Prospective Cohort	602	485	Adults infected with HIV, have never used ART, do not have a TB diagnosis	TB-LAM urin urine test	Liquid culture (reference standard) fluorescence microscopy and Xpert MTB/RIF	Sensitivity and specificity	2.62 (1.49 to 4.64)
Huerga et al. (2017)	Kenya	Prospective Cohort	805	474	Adults with HIV	LAM urine test	Smear microscopy, Xpert MTB/RIF and MTBC . test	Sensitivity and specificity	2.7 (1.50 to 4.90)
de Vasconcellos et al. (2021)	KwaZulu-Natal	Prospective Cohort	63	50	Critical patients are treated in the ICU King Edward VIII Hospital	LAM urine test	GeneXpert	Sensitivity and specificity	6.9 (1.70 to 28.30)
Gupta-Wright et al. (2019)	Afrika Selatan	Prospective Cohort	644	315	Adults infected with HIV	TB-LAM urin urine test	No urine test LAM	Sensitivity and specificity	1.8 (1.00 to 3.20)
Lawn et al. (2017)	Cape Town,	Prospective Cohort	585	427	HIV-positive adults	TB-LAM urin urine test	MGIT and/or Xpert MTB/RIF	Sensitivity and specificity	4.2 (1.50 to 11.75)
Manabe et al. (2014)	Uganda	Prospective Cohort	506	351	HIV-positive adults	LAM urine test	Cryptococcal Antienuresis	Sensitivity and specificity	2.29 (1.29 to 4.05)
Bjerrum et al. (2019)	Ghana	Prospective Cohort	575	532	Adults with HIV	FujiLAM urine test	AreleLAM	Sensitivity and specificity	4.8 (3.01 to 7.64)
Huerga et al. (2021)	Malawi	Prospective Cohort	580	387	HIV-infected adults with TB symptoms	LAM urine test	No urine test LAM	Sensitivity and specificity	2.5 (1.10 to 5.70)

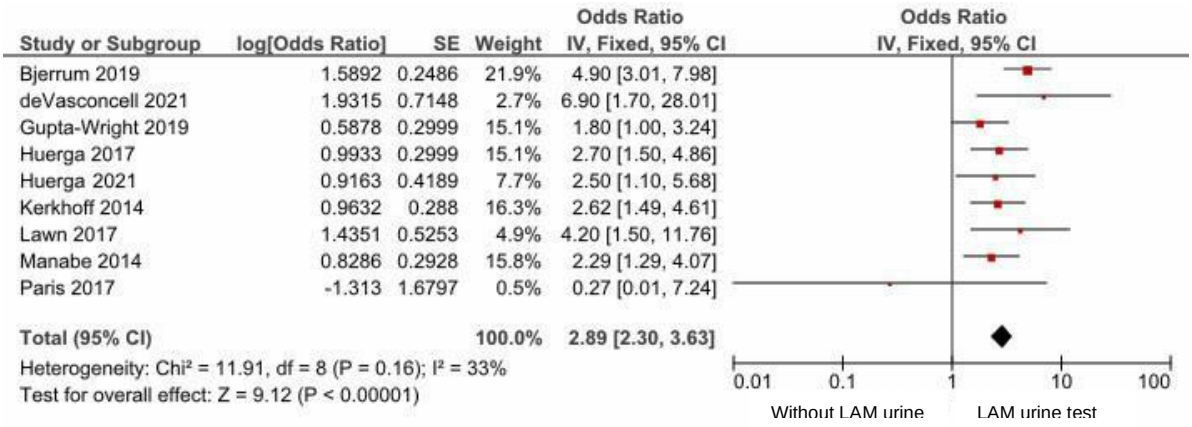

Figure 3. Forest Plot of the Accuracy of Lipoarabinomannan Urine Test in Diagnosing Pulmonary Tuberculosis in Adults

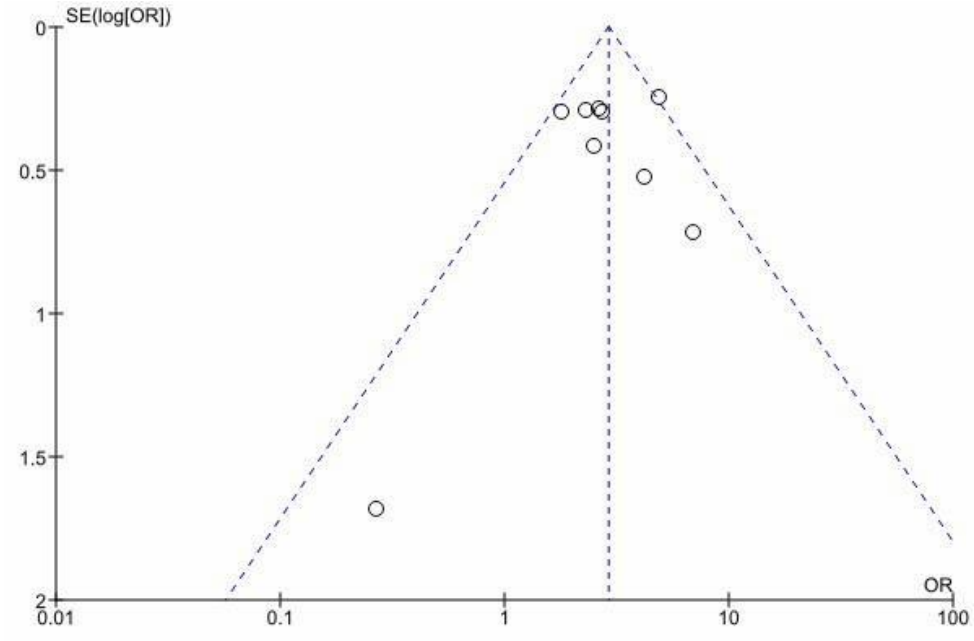

Figure 4. Funnel Plot of Administering Lipoarabinomannan Urine Test in Diagnosing Pulmonary Tuberculosis in Adults

DISCUSSION

A systematic study and meta-analysis of studies showed that the lipoarabinomannan urine test was 2.89 times accurate in diagnosing pulmonary tuberculosis in adults (aOR= 2.89; 95%CI= 2.30 to 3.63; p= 0.160) but was not statistically significant. This is in accordance with a study by d'Elia et al., (2015) which stated that a trial was conducted on HIV-positive patients without known TB at the time of initiation of ART, assessing the sensitivity, specificity and likelihood ratio of positive/negative LAM for predicting LAM. TB incidence within 6 months of starting ART, it was found that LAM had a poor sensitivity of 0.0% (95% CI= 0.00 to 23.2) for predicting TB incidence within 6 months of initiation. In addition, the investigators added that LAM has limited value for accurately predicting TB incidence in patients with higher CD4 cell counts after ART initiation. LAM can

help identify TB/HIV coinfected patients on ART who respond more slowly to treatment and require targeted interventions to improve treatment outcomes.

The results of another study conducted by Drain et al. (2014) of 342 HIV-infected participants, the researchers stated that the LAM urine test had a low sensitivity of 28.3% (95%CI= 17.5 to 41.4) with a specificity of 90.1% (95%CI= 86.0 to 93.3) for TB screening among adults newly diagnosed with HIV. However, when the LAM urine test was combined with sputum microscopy, the sensitivity increased to 38.3% (95%CI= 26.0 to 51.8) but the specificity decreased to 85.8% (95%CI= 81.1 to 89.7). Then in a study conducted by Balcha et al. (2014) it was found that the LAM urine test had poor performance for diagnosing TB in the adult population with HIV in Ethiopian health centers, but when combined with sputum microscopy, the LAM urine test could be considered. to diagnose TB in this subgroup.

Then in the results of a study conducted by Shah et al. (2014) among 103 participants with TB it was found that the Xpert sensitivity was superior (76%) than LF-LAM (49%) with a specificity greater than 97% for both tests, and the combined Xpert and LF-LAM tests have a sensitivity of up to 85%. The combination of the LAM urine test and the Xpert sputum test complement each other for diagnosing active TB in HIV-infected patients with superior sensitivity to the two tests when the tests are performed alone.

From the data above, it shows that although the LAM urine test has an accuracy of 2.91 times combined with easy and inexpensive sampling in diagnosing tuberculosis in adults with suspected TB, especially for people with HIV, the performance of the LAM urine test will be much better if combined with sputum microscopy in diagnosing TB. The drawback of this research is the bias in terms of language because the articles used are English articles. The publiccation bias is shown by the funnel plot results and the search bias is due to using only four databases.

AUTHORS CONTRIBUTION

Jihan Nafisah Fauziy and Kartika Febry Ana are researchers who choose topics, find and collect data and process research data.

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CONFLICT OF INTEREST

There was no conflict of interest in this study.

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