Journal of Research in Pharmacy

Research Article

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A systematic review and meta-analysis: the effect of pharmacist-led antibiotic stewardship programs on antibiotic consumption and rational use

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Received: 23 March 2023 / Revised: 25 June 2023 / Accepted: 07 August 2023

ABSTRACT: Irrational use of antibiotics and antibiotic resistance are one of the major problems encountered in healthcare services. Antibiotic stewardship programs (ASPs) have been one of the most successful attempts in hospitals to control antibiotic resistance. Pharmacists are the core health professionals in ASPs. This study aimed to examine the effect of clinical pharmacist-led ASPs on antibiotic consumption with meta-analysis. ScienceDirect, PubMed, MEDLINE and Cochrane databases were searched for relevant studies. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline was used to identify studies for the review. Methodological quality was assessed using Newcastle-Ottawa scale (NOS) and National Heart, Lung and Blood Institute (NHLBI) pre-post comparison studies quality tool. The R (version 4.0.3.) and metafor packages (version 2.1-0) were used for a random-effects meta-analysis. After pharmacist intervention, the pooled rational use of antibiotics was determined as 0.28 (28% improvement, I^2=98.26; 95% CI 0.15-0.41). The pooled duration of therapy data was determined as 0.41 (41% reduction, I^2=96.30%; 95% CI 0.54-0.29) in favor of the group with the pharmacist's intervention. As a result of this study, it was determined that clinical pharmacists took part in the evaluation of the patient, regulation of the treatment, follow-up of the patient after treatment, and education in ASPs. These findings can contribute to improving the role of the pharmacist in ASPs and rational antibiotic use, thereby controlling antibiotic resistance.

KEYWORDS: Antibiotic use; antibiotic resistance; duration of therapy; pharmacist-led antibiotic stewardship program; pharmacist intervention.

1. INTRODUCTION

Antibiotic resistance is one of the major problems encountered in healthcare services. It has become a threat to public health since there has been a decrease in the research and development of new antibiotics. Therefore, the treatment of diseases frequently seen in society is becoming more difficult and causing adverse consequences such as prolonged hospitalization due to antibiotic-resistant infections [1]. Antibiotic resistance is simply defined as the ability of microorganisms to survive in the presence of antimicrobial agents. The World Health Organization (WHO) has five goals in its global action plan on antibiotic resistance. These are the following [2]: to improve awareness and understanding of antimicrobial resistance; to strengthen knowledge through surveillance and research; to reduce the incidence of infection; to optimize the use of antimicrobial agents; and to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines, and other interventions.

Methods of combating antibiotic resistance are mainly based on restricting the use of antibiotics. These methods generally include not using antibiotics without prescription, prescribing antibiotics at the right indication, and controlling the use of antibiotics in agriculture and animal husbandry [3]. The most successful attempts to control antibiotic resistance are infection control programs, antibiotic stewardship programs (ASPs), and vaccinations administered for preventing the spread of resistant organisms within society [4].

It is aimed with ASPs to select and administer the antimicrobial treatment that would give the best clinical result in the treatment or prevention of diseases, would cause the least toxicity in the patient, would not increase antimicrobial resistance, and that would include the most appropriate dose and duration. Ideally,

How to cite this article: Aydın Guldur E, Karabulut E, Ozcelikay G. A systematic review and meta-analysis: the effect of pharmacist-led antibiotic stewardship programs on antibiotic consumption. J Res Pharm. 2024; 28(4): 912-922.

ISSN: 2630-6344
https://dx.doi.org/10.29228/jrp.2022.00

ASPs are based on a multidisciplinary approach studied by infectious disease specialists, microbiologists, and pharmacists [5]. Multifaceted strategies form the basis of ASPs. These are generally an educational intervention, implementation of guidelines for infection treatment and pre- and post-audits with a view to addressing the need for behavioral change [6].

The effects of ASPs are measured by different methods. The most commonly used ones are identification of the number of prescriptions containing antibiotics, identification of the amount of antibiotics consumed, number of susceptible bacterial strains and duration of treatment, development of secondary infection, patient-based determinations such as on whether it is necessary to re-use antibiotics within 30 days [7].

Drug counseling is one of the key elements of ASPs designed by the Centers for Disease Control and Prevention (CDC) in 2019. According to the CDC, consultant pharmacists should act as antibiotic specialist and program leader. The tasks undertaken by pharmacists within the antibiotic stewardship team are the following: preparation of guidelines on antibiotic use, follow-up of patients for optimization of treatment, provision of trainings on appropriate use of antibiotics, and follow-up and control of data on the use of antibiotic [8]. The aim of this study is to examine the effect of clinical pharmacist-led ASPs on antibiotic consumption with meta-analysis.

2. RESULTS

A total of 10747 records were identified through database searches. 3945 records were screened in total after removing duplicates. Of 35 potentially relevant articles reviewed in full text, 25 studies were included in the meta-analysis (Figure 1).

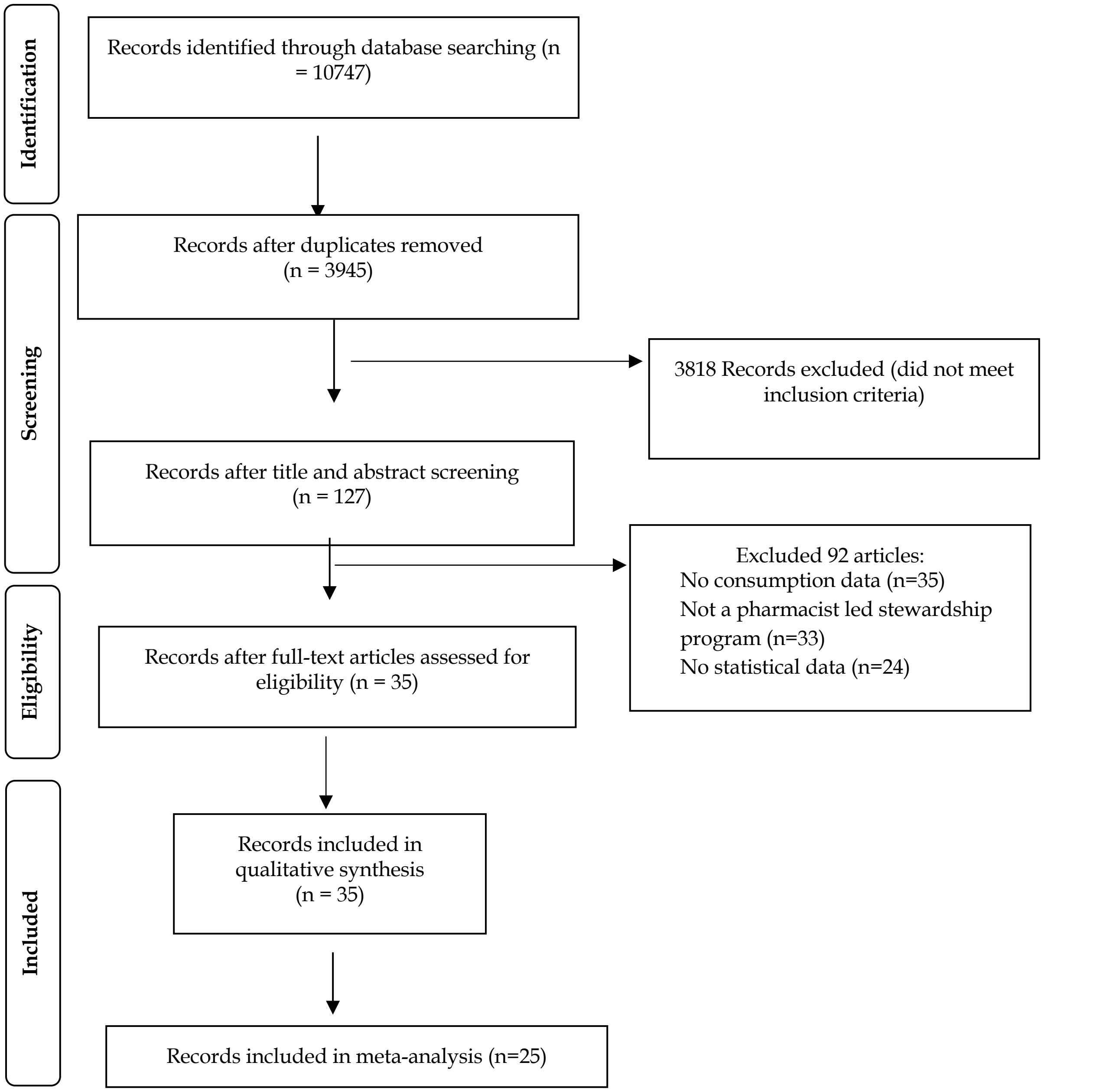

Figure 1. Study selection process for the effect of pharmacist-led ASPs on antibiotic consumption (adapted from PRISMA diagram).

2.1. Study characteristics

General information on the studies investigating the effect of pharmacist-led ASPs on appropriate antibiotic use and antibiotic consumption is given in Table S2 [11-28,46] and S3 [11-14,29-34] in the Supplemental Table. 19 studies were conducted on the measurement of the change in the appropriate use of antibiotics as a result of the ASP. There are 10 studies measuring antibiotic consumption by DOT/1.000 days.

There are 9 studies measuring antibiotic consumption by DDD unit. The studies included in the systematic review are given in Table S4 [12,15,35-44,47] in the Supplemental Table.

2.2. Quality assessment

Cohort studies were evaluated with the Newcastle-Ottawa scale [9]. The evaluation results are given in Table S5 in the Supplemental Table. No studies were excluded from the analysis as there were no studies with a quality score below five. The pre-post studies performed with no control group were evaluated with the NHLBI's quality assessment tool as shown in Table S6, S7 and S8 in the Supplemental Table.

2.3. Meta-Analysis

Appropriate use of antibiotics is defined in the literature as selecting the right antibiotic, in the right dose, and for the right duration. In the meta-analysis performed by calculating the risk difference, the result was obtained as 0.28 (95% CI 0.15-0.41) in favor of the group with pharmacist intervention (Figure 2). The heterogeneity (I^2) was 98.26% ($p<0.0001$). This finding indicates that the pharmacist's intervention in hospitals increases the rational use of antibiotics.

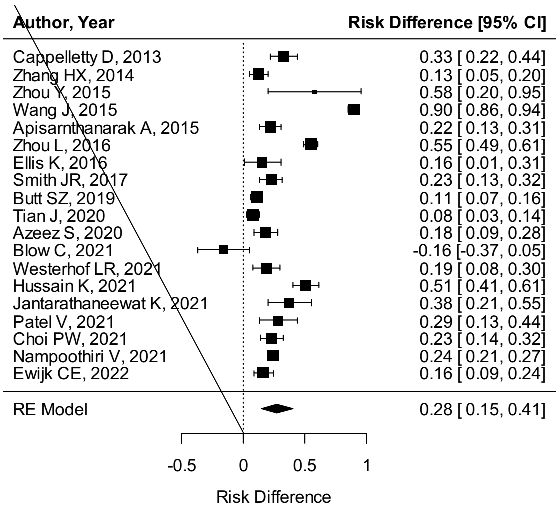

Figure 2. Forest plot of included studies (appropriate antibiotic use).

Studies examining the rational use of antibiotics were conducted on the continents of Asia and America. A sub-group analysis was performed to measure the difference between the continents. It was determined in the sub-group analysis that 7.41% of the heterogeneity (R^2) in the studies was caused due to the difference between the continents (Figure 3). Yet, no significant difference was found between Asia and America regarding the appropriate antibiotic use ($p=0.1095$).

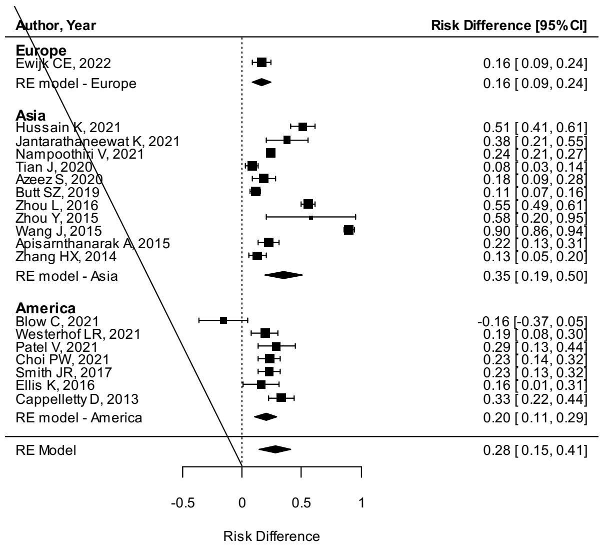

Figure 3. Forest plot of sub-group analysis.

The result of the meta-analysis performed by calculating the percentage change based on the studies measuring the DOT as a result of the pharmacist's intervention was obtained as 0.41 (95% CI 0.54-0.29) in favor of the group with pharmacist intervention (Figure 4). The heterogeneity (I^2) was 96.30% ($p<0.0001$). As recommended by WHO, DOT data is preferred to compare the consumption of antibiotics. According to this result, the pharmacist's intervention in hospitals reduces the duration of antibiotic therapy and antibiotic consumption.

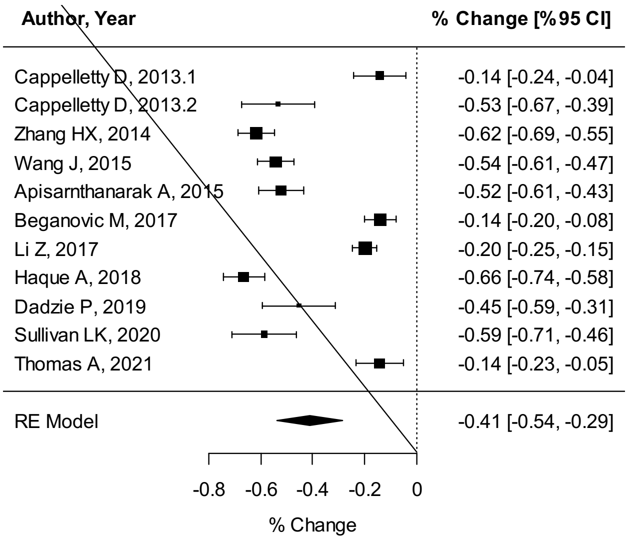

Figure 4. Forest plot of included studies (change in duration of therapy).

2.4. Qualitative synthesis about the effect of pharmacist-led ASPs on antibiotic consumption

In some of the studies [15,35,37-38,40,42,44,47], the change in total consumption was measured, while some of them [12,35-37,39,41,43] were conducted for antibiotic-specific assessments. When the consumption data for total and antibiotics were evaluated together, it was found that the consumption decreased following the pharmacist-led ASP in ten studies [12,15,35,37-38,40-42,44,47], and this change was found to be statistically significant ($p < 0.05$). In some studies [12,35-36,43-44], an increase was observed in the consumption of specific antibiotics. Of these data, only four [12,35,43-44] were found to be statistically significant ($p<0.05$). The increase in antibiotic consumption is interpreted as that restricting the use of a group of antibiotics can lead to an increase in other groups.

According to the results and the interventions in relevant studies, the role of pharmacists in pharmacist-led ASPs are summarized as follows (Figure 5):

https://dx.doi.org/10.29228/jrp.2022.00

Evaluation of the patient

- Participating in consultations with the relevant physician [35,37,41,44]
- Pre-evaluation of prescriptions [35,37,41,44]
- Examining and evaluating the patient's medical records and culture results [35, 37, 39]

Designation of the relevant treatment

- Determination of dose, duration of treatment and route of administration [35,38, 39]
- Deciding which antibiotic to use [12,37,39]
- Changing the use of antibiotics when necessary (such as switching from parenteral to oral use)[38,39]
- Notification of recommendations on therapeutic arrangements to the relevant physician (prospective audit and feedback) [12,15,38,40,42,43,44]

Patient monitoring

- Monitoring antimicrobial culture results after treatment [12,35,36]
- Monitoring drug interactions and adverse reactions [12,35,36,37]
- Monitoring the treatment period and terminating the treatment when necessary [12,37]
- Monitoring antibiotic consumption rates throughout the hospital [12, 15]

Training

- Training of antibiotic stewardship program team members [15,35,42,43]
- Preparation of guidelines regarding the use of antibiotics [15,42,43]
- Determination of restricted antibiotic lists [35, 42]

Figure 5 Role of pharmacist in ASPs

3. DISCUSSION

This study is the first meta-analysis study evaluating the effect of pharmacist-led ASPs on antibiotic consumption and rational antibiotic use. As a result of our study, it was observed that pharmacists took part in the evaluation of the patient, regulation of the treatment, follow-up of the patient following the treatment and education in ASPs. With the training, patients are informed about the appropriate use of the drug and guidelines for the appropriate prescribing of antibiotics are developed and explained to healthcare professionals. In half of the studies included in the analysis, pharmacists took part in prospective audit and feedback and treatment optimization tasks. These studies are followed by training activities and pre-authorization, i.e., restriction of the use of certain antibiotics. In a systematic review conducted by Satterfield et al. [46], training in ASPs was discussed under three headings. These are the training for the prescribing physician, the training for the ASP team and other health professionals, and the training for the patient. Pharmacists are defined as medical staff members who are obliged to take part in all steps of the training program. The role of pharmacists in liaising with other healthcare professionals in the development of antimicrobial guidelines are also supported by several studies [48,49]. Chetty et al. [50] reported that pharmacist specific intervention in public hospitals in South Africa included: advising a switch from intravenous to oral antibiotics, dose adjustments, dose optimization, time-sensitive stop orders for specific antibiotic prescriptions. Pharmacists are healthcare professionals who can evaluate antimicrobial treatment in a versatile way in terms of indication, drug selection, dosage, route of administration and duration of treatment. Pharmacists can change the type, dose and duration of the antibiotic, de-escalate the antibiotic used, terminate the treatment, switch from intravenous use to oral use as well as monitors the drugs taken in line with the relevant laboratory results, follows up drug-drug interactions and report all these to the infectious disease specialist. In a study coducted by Monmaturapoj et al. [51] it is indicated that involvement of pharmacists in ASPs has been shown to be associated with enhanced implementation success, improved patient outcomes as well as reduced antibiotic consumption and expenditure.

In the present study, it was observed that pharmacist-led ASPs reduced antibiotic consumption and treatment duration. It was found that there was an increase in rational antibiotic use in the ASPs after pharmacist intervention ($p<0.0001$). Similarly, the study by Mahmood et al. [52] demonstrated that pharmacist-led ASP showed a positive outcome in reducing inappropriate antimicrobial prescribing. In this review, the methods applied by pharmacists were not restricting the use of antibiotics, but rather the selection of the correct indication, the appropriate dose and the treatment period as well as the optimization of the treatment, the follow-up of the patient after the treatment and feedback to the physician. In a systematic review conducted by Otieno et al. [53] it is reported that pharmacist-led ASPs in both public and private hospitals contains education, audits and feedback, development of protocols and ward rounds. The findings of this review are comparable to previous reviews that indicated that ASP interventions improve antibiotic use [54,55]

Our review has limitations. First, we only reviewed the ASPs published in full papers and some programs might have been missed. Second, we only included outcomes of the patients in hospitals or clinics. However, antimicrobial stewardship might have longer-term benefits and a complete evaluation of the impact of ASPs would extend beyond hospitals or clinics where ASPs are implemented. These studies did not allow an assessment of the potential impact of ASPs on the society. Most of the studies examining the effect of pharmacist-led ASPs are pre-post comparison studies, and pre-post populations differ from one another.

4. CONCLUSION

Pharmacists were mostly involved in prospective audit and feedback, and treatment optimization. Furthermore, pharmacists take charge in the development of protocols and guidelines on the use of antibiotics and play a determining role in the antibiotic stewardship policy. They are also responsible for explaining the protocols and guidelines developed to healthcare professionals and patients. As a result of the systematic analysis conducted, it was observed that pharmacist-led ASPs in hospitals decreased the total antibiotic consumption ~~and consequently antibiotic resistance~~ and increased the rational use of antibiotics.

In the antibiotic stewardship model to be established, pharmacists should mainly take part in training, pre-treatment evaluation of the patient, regulation of the treatment and post-treatment evaluation of the patient. Surveillance data must be accessible to clinical pharmacists for monitoring. Effective communication between the physician and the pharmacist is of great importance in terms of achieving the goal of the program, as it is necessary to provide feedback to physicians regarding the treatment administered within the program.

5. MATERIALS AND METHODS

5.1. Search strategy

In order to determine the effect of pharmacist-led ASPs on antibiotic consumption, the following keywords were searched in the ScienceDirect, PubMed (MEDLINE) and Cochrane databases: "antibiotic resistance" or "bacterial resistance" or "antimicrobial resistance" or "antibiotic consumption" or " antibiotic stewardship program" and "pharmacist" or "pharmacist intervention".

5.2. Study eligibility criteria

The acceptance criteria in determining the effect of pharmacist-led ASPs on the consumption of antibiotics were established as follows: 1. The effect of the pharmacist's intervention on antibiotic resistance and/or antibiotic consumption should be stated; 2. No differentiation was made among the groups of antibiotics used and the types of bacteria to which resistance were developed.

In this study, we defined a pharmacist-led ASP as a hospital- or clinic-based program that included an intervention or a component the purpose of which was to reduce the consumption of antibiotics. The pharmacist-led interventions were defined as interventions where the pharmacist have the lead role in an intervention designed to reduce the consumption of antibiotics or to improve medication appropriateness.

The articles written in English were considered eligible. The selection strategy for articles in this review was adapted using the flow diagram from the Preferred Reporting Items for Systematic reviews and Meta-

Analyses (PRISMA) Statement. PRISMA checklist is presented in Supplemental Table. The titles and abstracts of articles were screened, and the reference lists of articles were also reviewed to identify eligible studies. Additionally, review articles and personal opinions were excluded. Data from January 2007-January 2023 were included for this review.

5.3. Data extraction

The studies considered to be eligible for inclusion were read in full and their suitability for inclusion was determined independently by two reviewers (E.A.G. and G.O.). Disagreements were managed by consensus. The data extracted included study characteristics (author, year of the study conducted, country, study design), the outcomes of the interest measured, the results related to these as well as intervention details.

For overall outcomes of the use of antibiotics, the indicators extracted were the standard indicators used to report antibiotic use: defined daily doses per 1.000 patient days (DDD/1.000 patient days) and duration of antibiotic therapy per 1.000 resident days (DOT/1.000 days). The indicators for the appropriateness of antibiotic use extracted were: the percentage of antibiotic prescriptions that were appropriate to treat an infection with an antibiotic (appropriateness of decisions to treat), and the percentage of antibiotic prescriptions where the appropriate antibiotic was selected (appropriateness of antibiotic selection).

For studies comparing the outcomes before and after the implementation of an ASP, in cases when the pre- and/or post implementation periods were divided into shorter time periods, we extracted the data in the period immediately before the implementation, which is the most comparable data to the data of the post-implementation period, and it is the latest period after the implementation to examine the long-term effect.

5.4. Quality Assessment

The quality of the cohort studies was evaluated with the Newcastle-Ottawa scale (NOS) [10]. The quality assessment tool of the National Heart, Lung and Blood Institute (NHLBI) was used for pre-post (before-after) comparison studies performed with no control group [10]. E.A.G. and G.O. conducted independent screening of the eligible articles. Subsequently, the resulting analyses were compared. When there was no consensus between the reviewers, another independent reviewer made the final decision on the analysis.

5.5. Data synthesis and meta-analysis

The R (version 4.0.3.) and metafor packages (version 2.1-0) were used for a random-effects meta-analysis to draw forest plot and calculate pooled results with 95% confidence interval (CI) and I^2 value.

Acknowledgements: None

Author contributions: Concept – E.A.G, G.O.; Design – E.A.G, E.K, G.O.; Data Collection and Literature Search– E.A.G, G.O.; Statistical Analysis– E.K.; Writing – E.A.G., G.O

Conflict of interest statement: The authors declared no conflict of interest

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