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SYSTEMATIC REVIEW

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Association between delayed initiation of treatment indications and survival in patients with cervical cancer: a systematic review and meta-analysis

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Abstract

This review evaluated the association between delayed time to initiate any treatment with survival in patients with cervical cancer. An internet-based literature search was performed in PubMed/Medline, Cochrane CENTRAL, EMBASE, Web of Science and Scopus databases. All articles published until December 2021 were included. Studies were pooled for meta-analysis in a random-effects model. Microsoft-Excel and the R programing software were employed in the analysis. Between-study heterogeneity was assessed using Q^2, I^2 and tau^2. Results were reported as a function of 4-week delay in treatment initiation and hazard ratio using forest plots at 95% confidence interval. A $p < 0.05$ was considered statistically significant. Eleven studies were included in this review, comprising 50,590 patients. Overall survival was evaluated based on the pooled effect of 11 comparison groups. The subgroup on five-years follow-up following radiotherapy revealed that a 4-week delay in treatment was associated with a 1.27 times higher rate of mortality (Hazard Ratio: 1.27; 95% Confidence Interval: 1.12–1.45). However, a 4-week delay in initiation of combined chemoradiotherapy (HR: 1.31; 95% CI: 0.76–2.23) or surgery (HR: 0.96: 95% CI: 0.60–1.54) did not predict a statistically significant rate of mortality. The same length of waiting time did not predict the rate of mortality in a 3-years follow-up period (HR: 0.76; 95% CI: 0.44–1.32). A 4-week delay in radiotherapy showed a 1.72 times higher rate of disease relapse in the delayed group (HR: 1.72; 95% CI: 1.25–2.35) but not in patients for whom surgery was performed (HR: 0.89; 95% CI: 0.75–1.04). A four-week delay in initiating radiotherapy was associated with a higher rate of mortality. On the other hand, a 4-week delay in initiation of either surgery (hysterectomy) or chemoradiotherapy does not appear to be associated with overall survival, probably accounted, partially, for the waiting time paradox.

Keywords

Cervical cancer; Delayed time to treatment initiation; Survival; Systematic review and meta-analysis

1. Background

Carcinoma of the cervix, also known as cervical cancer, is one of the public health concerns affecting women globally. Depending on its histological characterization, there are two main types of this condition. These are squamous cell carcinoma (SCC) with sets of differentiation occurring in 70% to 80% of the diagnoses, and adenocarcinoma, is common in about 10% to 15% of the cases [1]. The human papillomavirus (HPV), notably its 16 and 18 genotypes, is the predominant cause in the majority of patients with cervical cancer [2]. Even though incidence cases in the age group below 50 had been on the rise until 2018 [3], HPV-based screening [4] and vaccination [3, 5] campaigns have shown greater improvement in prevention efforts.

Though the distribution of cervical cancer differs by geographic regions and the sociodemographic index of populations, there have been an estimated 604,127 cases and 341,831 deaths worldwide in the period 1988 through 2017, according to a report in 2020 [6]. With this, cervical cancer stands as the fourth most common type of cancer in women [7]. It was also the first cause of cancer-related deaths among women in the sub-Saharan African region [7].

Treatment modalities for patients with cervical cancer largely depend on the stage of diagnosis and include surgery, chemotherapy, radiotherapy, or combination therapy [5]. Detection at early FIGO (International Federation of Gynecology and Obstetrics) stages (IA, IB and IIA) of the disease has the advantages of several management options, generally offered with radical hysterectomy with lymphadenectomy, radiotherapy, or chemotherapy depending on age, size of the tumor, comorbid status, stage of the

disease, or patient preference [8]. For patients with stages IIB to IVA, definitive chemoradiotherapy (CRT), involving weekly or triweekly cisplatin and external beam radiotherapy, is regarded as the standard of care [9]. According to a recent systematic review, immunologic agents, such as bevacizumab and pembrolizumab, administered with chemotherapy, showed acceptable safety and promise in treating patients with recurrent or metastatic cervical cancer [10].

Delay in treatment initiation has been described as a known contributor that determines the rate of remission or survival in cervical cancer [11, 12]. Yet, there is no clearly defined and agreed-upon evidence on the magnitude of the risk of experiencing mortality following a determined delay of treatment initiation, usually one month. Some studies also argued that the effect of shorter [13] or even longer [14] waiting times on survival might be minimal or not significant. A cautious understanding of delays, especially when the gap from diagnosis to treatment initiation becomes huge, is highly important. Given the existing challenges to carrying out high-quality studies and the fact that many national health programs are facing limitations in practicing strong empirical guidelines, evidence from systematically pooled primary studies might provide an up-to-date insight. And, despite the interplay of additional factors, there needs to be a concise understanding of the degree and direction of effect segmented by patient as well as treatment protocols.

This systematic review and meta-analysis is, therefore, aimed to producing evidence on the effect of delay from diagnosis to the initiation of appropriate treatments on overall survival or recurrence among patients with cervical cancer.

2. Methods

2.1 Search strategy

The search strategy employed the use of keywords, index/mesh terms, truncated words, and references from other studies (snowballing) to ensure a maximum possibility of including all eligible articles. Searching was facilitated using the Boolean operators (AND/OR) in the respective sources. Bibliographic searches in PubMed, EMBASE, Cochrane Central, Scopus, Web of science were performed. Similarly, gray literature sources, such as Google Scholar, Networked Digital Library of Theses and Dissertations (NDLTD), and Dissertations and Theses Global, including those unpublished, were searched. There was no limit on the start date, and both English and non-English articles published earlier until December 2021 were considered. Furthermore, both forward and backward reference searching methods were used to locate all potential references (see **Supplementary Table 1**).

2.2 Eligibility and exclusion criteria of included studies

All available observational studies and interventional designs (if the latter may be available in exceptional circumstances, such as planned delays during pregnancy), were considered. The eligibility of studies and populations in the review was based on a consideration of the following criteria: (1) All patients diagnosed and histologically confirmed with primary cervical cancer of any stage, and were treated with chemotherapy, surgery, radiotherapy and/or any combination of these, either as concurrent or sequential deliveries. (2) The time frame between diagnosis and treatment initiation was clearly known, and survival outcomes of any form (disease-specific or overall) were reported. (3) Studies rated as "good quality" based on the Newcastle-Ottawa Scale and those fulfilling all the following criteria were included; (a) studies analyzed with clear comparator groups, and (b) studies that reported the effect of delayed treatment initiation adjusted for other prognostic factors. (4) Studies published until December 2021 were included. To reduce publication bias, all observational studies, either in full-text, abstract, correspondence or letters to editors, dissertations, or meeting abstracts, were eligible. There was no language restriction, but studies other than English should have at least included abstracts published in English. When accessing full text was impossible, authors were requested *via* email. On the contrary, studies that assessed the effect of delay in other forms of treatments, such as immunotherapy, palliative care, and behavioral treatment (psychotherapy, cognitive behavioral therapy) options, hyperthermia (in patients receiving radiotherapy), or findings reported in other measures of effect size (relative risk or risk ratio, odds ratio or correlation), were excluded if sufficient data was not available to calculate hazard ratios or results ignored the importance of time in the outcome.

2.3 Quality assessment of the included studies

Commonly referred to as the risk of bias assessment [15], this approach was utilized to scrutinize and ensure the internal validity of the potential studies. Initially, essential procedures such as protocol registration [16], development, and publication [17] were carried out in accordance with a suitable guideline [18]. Subsequently, all studies meeting the initial inclusion criteria were systematically assessed for their methodological quality. The "Newcastle-Ottawa risk of bias assessment scale" [19] for nonrandomized studies was employed for this purpose. There are commonly recommended steps to be followed in reporting systematic review and meta-analysis results. The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" [20] checklist has well been known for reporting randomized controlled trials (RCT) and observational study-based reviews (see **Supplementary Table 2**). In addition, the steps stipulated in the "meta-analysis of observational studies in epidemiology (MOOSE)" [21] (see **Supplementary Table 3**) were followed for the reasons of suitability to assess publication bias, a characteristic common in observational studies [18]. It also allows for inclusive searching considerations, such as the inclusion of non-English-language articles.

2.4 Screening and data extraction procedures

Collated studies and abstracts were screened at a title, abstract and full text level using the Rayyan web-based application [22] before data extraction commences. Keywords of inclusion used in the package were: time to treatment, delayed treatment initiation, overall survival, diagnosis to treatment, survival in

cervical cancer, and cervical cancer. Three reviewers were involved to accomplish the screening, quality assessment, and data extraction processes. While two of the reviewers (TS and BG) were involved independently, the third reviewer (TG) was consulted at times when disputing results arose between the other reviewers. Data on study designs, treatment type, time delayed alternatively used as waiting time, summarized age of patients (as mean, median or/and range), stage of cancer, quality assessment, authors and year of publication, follow-up period, outcome either as HRs or percentage and their 95% confidence interval, and number of patients per waiting time group were extracted.

2.5 Exposure and outcome measures

Exposure was the delayed time to initiate any recommended treatment (chemotherapy, radiotherapy, surgery or any combination of these, such as chemo-radiotherapy). It is counted as any unit of time from a histologically (biopsy) confirmed diagnosis. In cases where waiting time was reported at different patient contacts, such as biopsy confirmation and physician consultation, only the biopsy confirmed dates were considered. The delayed time of interest considered as "exposure" in this review was a 4-week delay computed from diagnosis to receiving treatment. The reference was a less than 4-week timeline from diagnosis to receiving treatment. In addition, more weeks of delay (8-week and 12-week) were also considered for comparison purposes. Evaluating the effect of a 4-week waiting time on survival has become increasingly common in systematic reviews of cancer research [23, 24] considering it the minimum appropriate time to detect clinically significant changes. This time frame also helps to scale the reported waiting times as an array of continuous measures that do not throw away information. The treatment effect of a 4-week or greater delay on overall survival (OS), is reflected using a hazard ratio from time-to-event analyses. OS events were captured using either a three- or five-year follow-up period. The terms "disease-free survival, disease-specific survival, recurrence-free survival, or relapse-free survival" were treated as disease free survival (DFS) which counts from the date of starting a treatment to the date of an event (relapse) or censoring (including death). As all included studies did not report the effect of treatment delay on survival uniformly, a method to convert study-specific HRs measured against diverse timelines into less or greater than 4-week delay, has been necessary. The upper and lower boundaries of the 95% confidence intervals of reported HRs were used to back-calculate standard errors for the log-HRs used in our analyses. The adjusted log-HRs were divided by the number of weeks in the reported waiting time of each study to estimate weekly study-specific log-HRs which were then included in the meta-analysis. Finally, the pooled log-HRs were converted to HRs as a function of a 4-week delay in treatment initiation. Study-specific HRs, either OS or DFS, along with their 95% confidence intervals, were computed and reported (see **Supplementary material 1**).

2.6 Meta-analysis

A quantitative data synthesis was performed in Microsoft Excel and a set of R packages. Initially, extracted data tabulations were entered into MS-Excel, manually cleaned, formatted and sorted. Next, the collated data was transferred into the R programming software version 4.3.1 (R Core Team, Vienna, Austria) [25]. Study-specific log-HRs representing the effect of a greater as opposed to a less than 4-week delay in treatment was pooled across studies and the pooled log-HRs were converted to HRs. The pooled log-HRs were obtained using random effects meta-analysis, taking into account each study's standard error of the effect estimate. A graphical presentation of study-specific waiting times against HRs was visualized using the "ggplot2" package in the "tidyverse" collection. The "meta" and "dmetar" packages were used in the estimation of pooled log-HRs (using the "metabin" function) and corresponding HRs in forest plots as well as the identification of influential studies. To test the presence of influencing factors with the observed pooled estimate, a univariable and multivariable meta-regression was performed using the "mvmeta" package. Alternatively, a multi-model inference analysis was undertaken to identify the most influential moderators in the list. A log linear relationship with waiting times was assumed in a random-effects model, and the dependent variable was the study-specific log-HR weighted by its variance. Results were presented in tables, figures and forest plots with 95% confidence intervals. A prediction interval was also added in the model to estimate the possible interval that future observations may account for.

Different tests, including Cochran's Q squared, I squared and tau squared were employed to estimate the degree of variation across the included studies. While there are limitations in the estimates of between-study heterogeneity applying each metric [26], reporting all is deemed substantial to ease interpretation as well as speculate over the possible source of variation not accounted for by a sampling error alone. A subgroup analysis was carried out depending on heterogeneity of studies, and the type of treatment indication, such as chemotherapy, chemoradiation, surgery and radiotherapy, patients received. Potentially influencing factors, namely treatment type received, follow-up period, proportion of patients with adenocarcinoma, proportion of patients with stage III or higher, and sample size of individual studies were tested in the meta-regression. A sensitivity analysis was carried out by omitting individual studies at a time using a leave-one-out method. Publication bias was assessed using funnel plots generated in Review Manger (RevMan 5.3, The Cochrane Collaboration, Copenhagen, The Nordic Cochrane Center, Denmark) [27] and the degree of asymmetry was determined using Egger's test in R. A $p < 0.05$ was considered statistically significant in all analyses. To precisely operationalize the concepts "exposure" and "outcome" defined earlier, the reviewers used the terms "treated" and "delayed" in figures and texts to referring the relative rate of mortality or recurrence among lesser waiting time (reference) and greater waiting time (exposed) groups respectively.

3. Results

3.1 Study screening and selection

As shown in the figure below, study identification was performed using database searching and other methods. A total of 630,904 articles were located using the database search, such as PubMed, Cochrane Central, and EMBASE. After checking and removing duplicates (n = 158) in a reference manager (EndNote.7), 629,247 items were removed for other reasons, such as an automatic keyword search assisted with manual inspection in Rayyan software (The Rayyan Systems Inc., Cambridge, MA, USA) [22]. Further, we eliminated 1476 articles after checking their titles and abstracts, which finally retained 5 articles for inclusion. On the other hand, gray literature and citation or reference searching were carried out, producing an additional six items. Overall, 11 studies [11–14, 28–34] were identified for our analyses among which we were able to identify18 comparisons for the analysis of treatment delay for either OS or DFS. There were 14 OS comparisons and 4 DFS comparisons. There were more than 11 OS comparisons because two studies reported outcomes evaluated on more than one treatment waiting time. The following three studies, comprising one comparison group each, were excluded from the meta-analysis. The study by Dereje *et al.* [31] was only a 3-year follow-up evaluation of patients receiving radiotherapy given that other studies in the meta-analysis were based on a 5-year follow-up. On the other hand, the type of treatment patients received was not vividly defined in the study by Chen *et al.* [11]. Lastly, in the report by Shen *et al.* [28], it was stated that the patients received all conventional cancer treatments, namely radiotherapy, surgery, and chemoradiotherapy, which poses difficulty in grouping the treatment (Fig. 1).

3.2 Characteristics of included studies

Ten of the 11 articles included in this review were based on a retrospective (historical) cohort design, except one study, which was a prospective cohort [31]. The studies comprised 50,590 patients in total, ranging from a sample size of 183 [31] to 12,603 [33]. All studies were rated as "good quality" based on the Newcastle-Ottawa scale [19] for risk of bias assessment. However, the proportional hazard assumption test was documented only in a few [12, 31, 32] of the studies. Geographically, 4 of the studies were done in Asia [11, 13, 29, 33], 4 in North America [12, 30, 33, 34], 1 in Africa [31], 1 in the Middle East [14], and 1 in South America [29]. Seven studies reported a median age between 44 and 55 years, while the remaining 4 studies reported the mean age of participants ranging from 45.9 to 65.38 years. The stage of cancer evaluated in 9 of the included studies was I to IV [11–14, 28–31, 34], and stages I to II in the remaining two [32, 33]. The types of treatment patients received were radiotherapy in 3 studies [29, 31, 34], surgery in 2 studies [32, 33], and CCRT in 5 studies [11–14, 29]. There was no information on what specific treatment patients received in one study [11]. Meanwhile, eight studies [12, 13, 28–30, 32–34] were documented to evaluate OS with a follow-up of 5 years across all treatments. Of these, the study by Nanthamongkolkul *et al.* [32] included a comparison group that extended the assessment of survival after five years. Three studies [11, 14, 31] evaluated OS in three-year follow-up under CCRT only. Similarly, DFS was reported in two studies [32, 34]. There was inconsistency in considering waiting time for treatment initiation across the studies, ranging from a median of two weeks to 30 months (**Supplementary Table 4**).

The study-specific hazard ratios (HRs) and the corresponding waiting times (weeks) of 11 studies are shown in Fig. 2A. The range is based on waiting time intervals in the respective studies. The comparison groups in one study included differing effect measures, whereby the groups in the 5-year or less follow-up revealed an indifferent rate of mortality between the treated and delayed groups. On the contrary, the second comparison group that was followed for more than 5 years experienced an increase in risk of mortalities. As shown in Fig. 2B, the sketch for studies with two waiting time groups remains the same between the two graphs. However, the log-HRs for studies with more than two categories of waiting time were estimated using the weighted least squares in meta-regression. Further, studies that reported on more than one comparison group, such as based on different waiting times or outcomes of interest (OS *vs.* DFS), were suffixed independently with Roman numerals (Fig. 2).

3.3 Overall survival

There is a significant level of between-study heterogenity presented with purely negative and positive effect sizes among the included studies. Due to the fact that interpreting the higher tau^2 would be difficult from a practical point of view, a prediction interval was added to the model in order to suggest a possible directional change for the true 4-week wait time effect. This was generated only for the pooled estimate of the random effects, as the number of studies in the subgroups was very low.

Overall survival was evaluated based on the pooled effect of 11 comparison groups using a random-effects model. Though many potentially influential moderators (*i.e.*, treatment type received, follow-up period, proportion of patients with adenocarcinoma, proportion of patients with stage III or higher, and sample size of individual studies) were tested in meta-regression, most did not reveal a statistically significatnt contribution to the model. The second moderator (follow-up period) explained the variability in the effect size by 28.3%, substantially higher compared to the first moderator (RT or CCRT *vs.* Surgery) which was very low at 2.8%. Adding all factors to the last model resulted in only a slight improvement (R squared = 32%), with the unaccounted level of hetrogenity still being substantial (I squared = 98%). The multimodel inference analysis also placed the follow-up period at the top. A detailed description of the multivariable meta-regression report has been presented in (**Supplementary Table 5**) attached under the supplementary files. Because merging groups on radiotherapy and combined chemoradiotherapy could not be assumed to be the same from a practical point of view, we separated these options and evaluated them based on a follow-up period. Accordingly, the subgroup on five-year follow-up following radiotharpy revealed that a 4-week delay in treatment was associated with a 1.27 times higher rate of death from

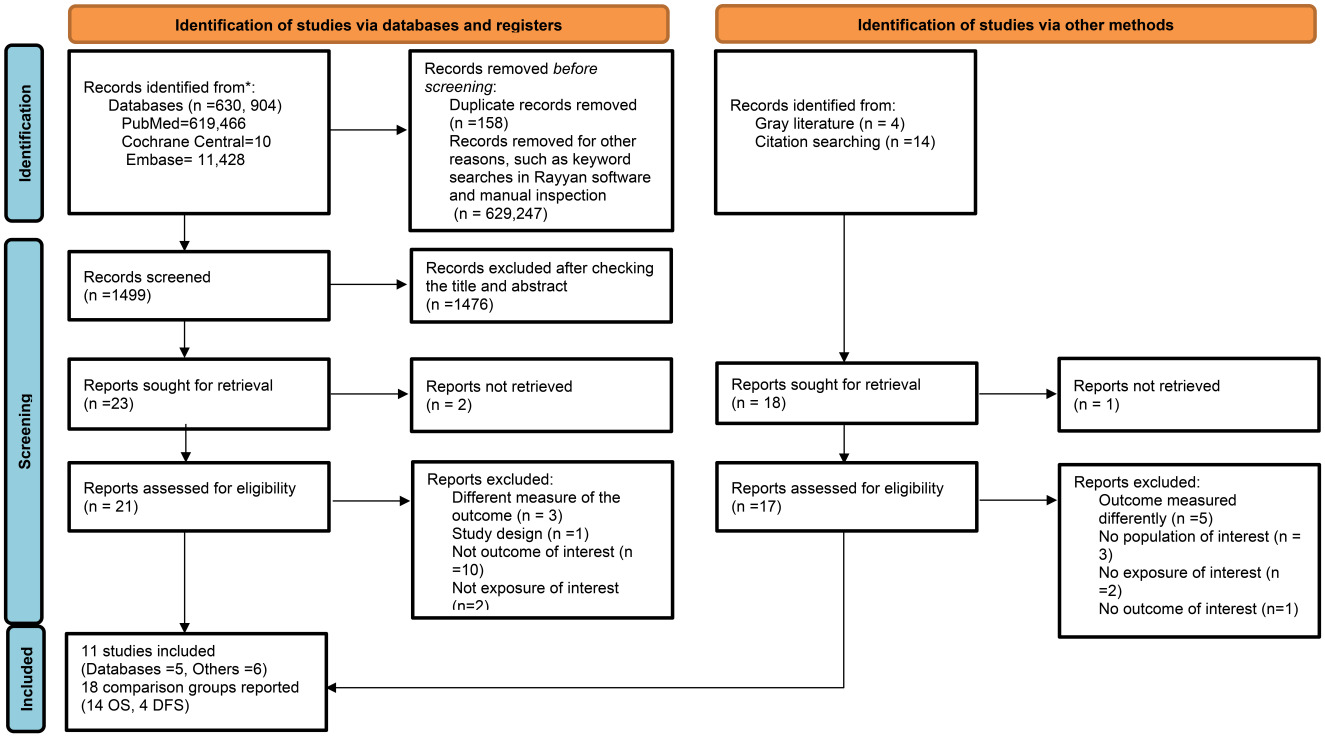

FIGURE 1. PRISMA 2020 flow diagram for included studies.

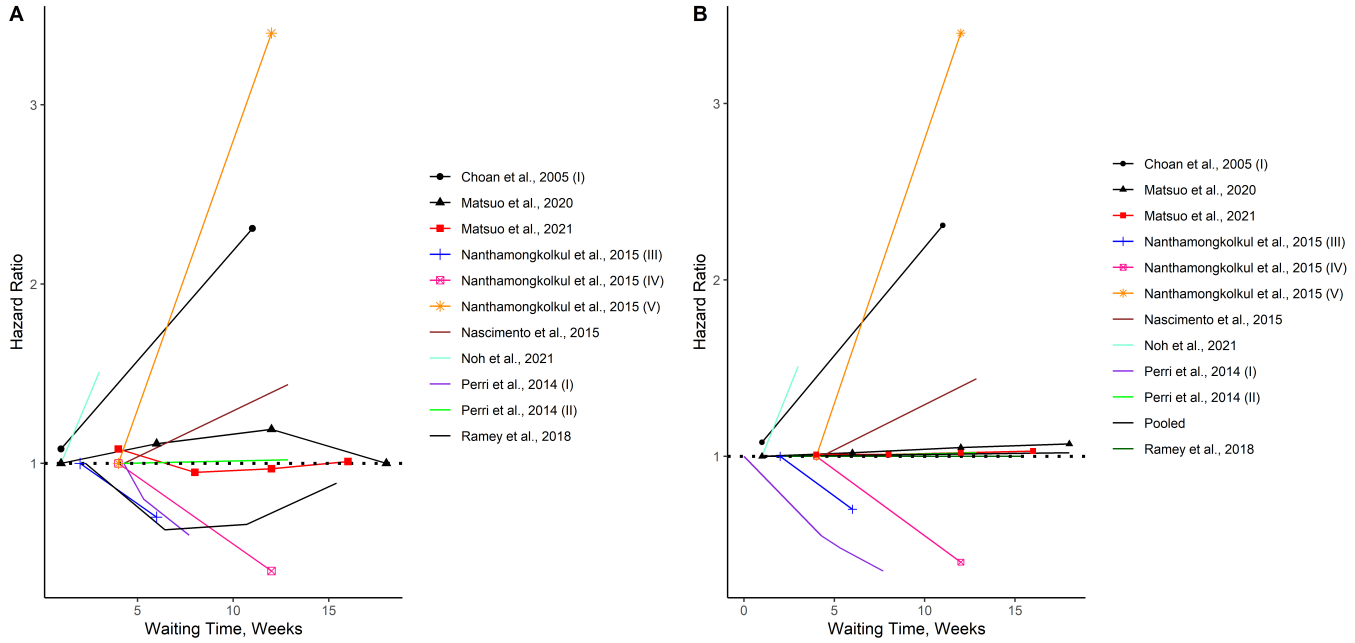

FIGURE 2. Study specific hazard ratios of overall survival plotted against waiting time in weeks. The plot shown in A represents the individual hazard ratios versus waiting time in weeks. The end of lines reflect effect estimate at the reported exposure time compared to the first waiting time category. Plot in B shows, computed hazard ratio per weekly delay of waiting time. The slope of each line indicates a change in logHR per a week of delay. For studies with more than two categories, weekly beta was estimated using a weighted least squared regression.

any cause (HR: 1.27; 95% CI: 1.12–1.45). Similary, evaluation of 8-week and 12-week delay in initiation of radiotherapy showed a 1.61 (95% CI: 1.24–2.09) and 2.04 (95% CI: 1.39–3.01) times higher rate of mortality, respectively, as compared with the non-delayed groups (**Supplementary Fig. 1A,B**). Nontheless, a 4-week delay in initiation of CCRT (HR: 1.31; 95% CI: 0.76–2.23) and surgery (HR: 0.96: 95% CI: 0.60–1.54) was not associated with a statistically significant increase in the hazard of death as compared with the group treated before 4 weeks after diagnosis. In parallel, the same length of waiting time did not predict the rate of death in a 3-year follow-up period (HR: 0.76; 95% CI: 0.44–1.32) (Fig. 3). Neither the 8-week or 12-week delay in treatment initiation among the remaining subgroups nor the overall pooled effect revealed any increased rate of mortality as compared with the respective non-delayed groups. As also depicted in the drapery plot, the effect of a 4-week waiting time on overall survival was assessed at different *p*-values. As the confidence level decreases and the *p*-value increases, we note that the confidence interval for the pooled effect gets narrower. The graph also shows study-specific confidence intervals for each 4-week delay in treatment (Fig. 4).

3.4 Disease free survival

As depicted in Fig. 5, the five-year follow-up report revealed that a 4-week delay in radiotherapy may also result in a 1.72 times higher rate of disease relapse (HR: 1.72; 95% CI: 1.25–2.35). However, the stated waiting time for surgery did not show any significant difference between the delayed and treated groups in the five-year period (HR: 0.89; 95% CI: 0.75–1.04) (Fig. 5). In the same way, the effects of either an 8-week or 12-week delays have been measured. The result showed that 8-week and 12-week delays in initiation of radiotherapy were associated with a mortality rate of 3.07 (95% CI: 1.64–5.74) and 5.37 (95% CI: 2.09–13.75), respectively, as compared with the non-delayed groups. Meanwhile, there was no effect difference noted either in the pooled estimate or surgery-received group for the assessed wait times (**Supplementary Fig. 1C,D**).

3.5 Publication bias

Apart from the graphical presentation to depict the plot of the hazard ratio against its standard error (se of logHR) shown below, a statistical method of detecting publication bias using Eggers' test was performed for the overall survival. The test does not indicate the presence of funnel plot asymmetry (intercept: −3.38; 95% CI: −19.55 to −12.80; t: −0.41; p = 0.69) (Fig. 6).

3.6 Influence analysis

As shown in Fig. 7, an influence analysis was carried out using the leave-one-out method to detect potential studies with a significant impact on the pooled effect size. Accordingly, removing two studies, namely Nanthamongkolkul *et al.* [32] (V) and Noh *et al.* [13], independently showed that the pooled effect size would change in the negative direction but was not statistically significant. The former compared the 8-week delay of surgery to post-5-year survival, while the latter assessed presumably 5-year survival following a 2-week delay. The total estimate at the base of the influence array indicates the overall pooled estimate when retaining all items (Fig. 7).

4. Discussion

In this review, we evaluated the effect of a greater as opposed to a less than 4-week wait from diagnosis to treatment initiation on overall survival in patients with cervical cancer. Due to the complexity and interaction in treatment type, stage of cancer, and follow-up period across the included studies, considerable heterogeneity was noted in this review. Indeed, the issue of heterogeneity is always inevitable in meta-analysis, as studies bring diversity clinically and methodologically [35]. From the results across all subgroups, it would be anticipated that statistically significant heterogeneity occurred, partly accounted for by sampling errors. This is likely because, in addition to the small number of studies included in each subgroup, there were studies with very small sample sizes [14, 32, 34]. Alternatively, an additional metric (I squared statistics) has been considered to assess the amount of variation that might not have been accounted for by sampling errors. This test still suggested a substantial degree of variation. With this, a number of reasons in individual studies would be mentioned as having a contribution. The characteristics assessed were: follow-up period, age distribution, treatment type received, stage of cancer, type of carcinoma, and sample size (**Supplementary Table 5**).

One of the comparison groups in the study by Choan *et al.* [34] and the study by Nascimento *et al.* [29] who received radiotherapy were evaluated. It was found that the proportion of stage III or higher cases was lower in the former (23% *vs.* 39%), whereas the percentage of 5-year OS was higher (53% *vs.* 23%). On the contrary, the rate of mortality in the former was higher than what was reported in the latter. Apart from the disparity in sample sizes, there could be a variation in terms of confounding events, possibly non-cancer-related mortality, among the delayed group in the first and the non-delayed group in the latter. Hence, relying merely on the aggregated proportion of stages of cancer or OS might be misleading. A similar variability persists in the subgroup assessed for CCRT as 5-year OS [12, 13, 30]. Despite similarities in mean age and treatment type received, the studies exhibited considerable heterogeneity. This would be owed, possibly, to the proportion of cases with stage III or higher cancer (53% in the study by Matsuo *et al.* [30], 2021 *vs.* 23% or 39.3% in the rest) and the proportion of cases with adenocarcinoma (0% in the study by Ramey *et al.* [12], 2018 *vs.* 11% or 12% in the rest). Meanwhile, the level of precision among the studies would still account for a significant part of the variation (chi squared = 88.5, df = 2, $p < 0.01$), as the study by Noh *et al.* [13] had the smallest sample size (389 *vs.* 5105 or 12,237 in others). In the same study, we also assumed that cases were followed for at least five years as it was not reported vividly (since enrolment was between 2001 and 2017 and the report was published in 2021), which could account for the unexplained possible variation.

Similarly, in the studies that considered patients for whom

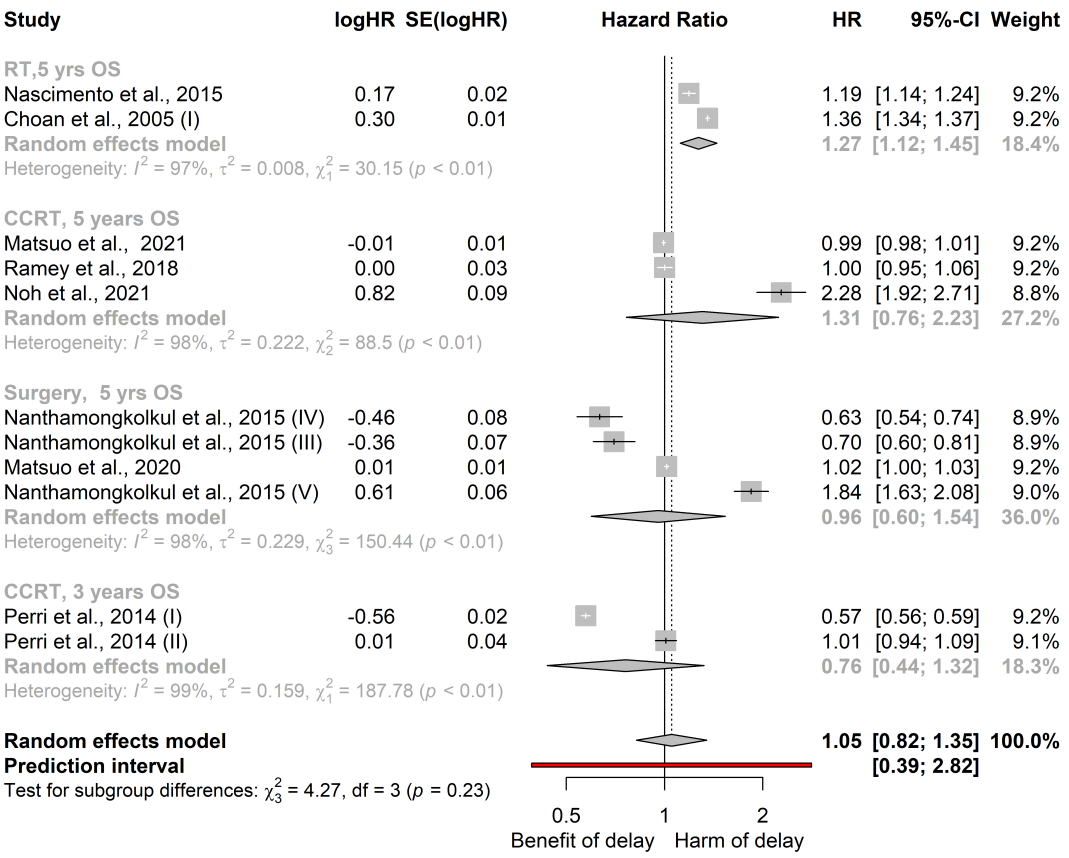

FIGURE 3. Subgroup meta-analysis of overall survival with a 4-week waiting time in patients with cervical cancer. SE: Standard Error; HR: Hazard Ratio; CI: Confidence Interval.

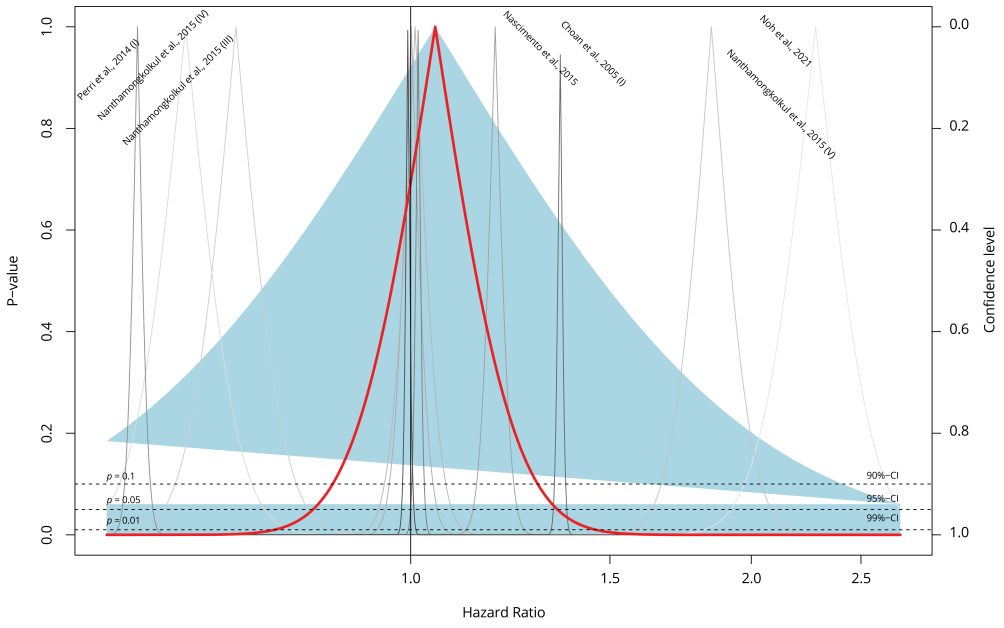

FIGURE 4. Drapery plot showing the association between 4-week waiting time and OS in cervical cancer at different *p*-values.

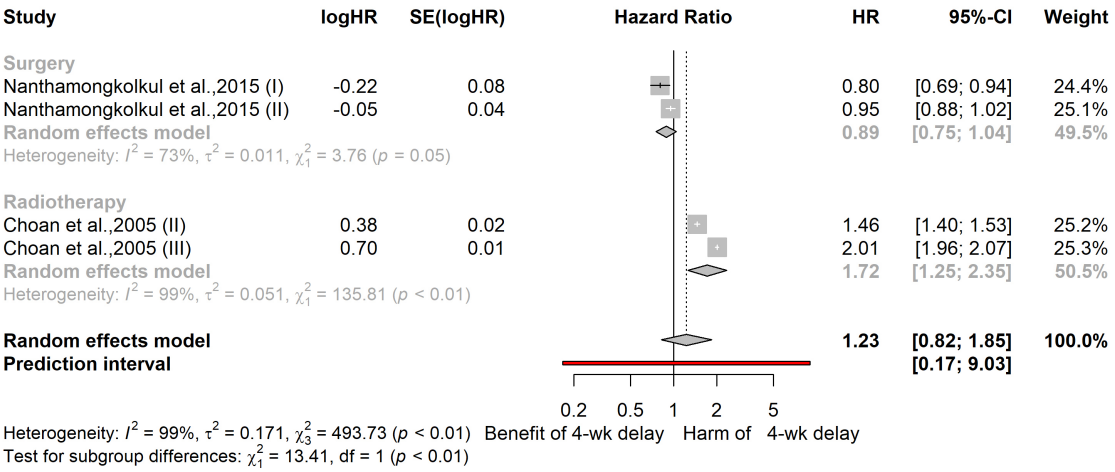

FIGURE 5. Subgroup meta-analysis of disease-free survival with a 4-week waiting time in patients with cervical cancer. SE: Standard Error; HR: Hazard Ratio; CI: Confidence Interval.

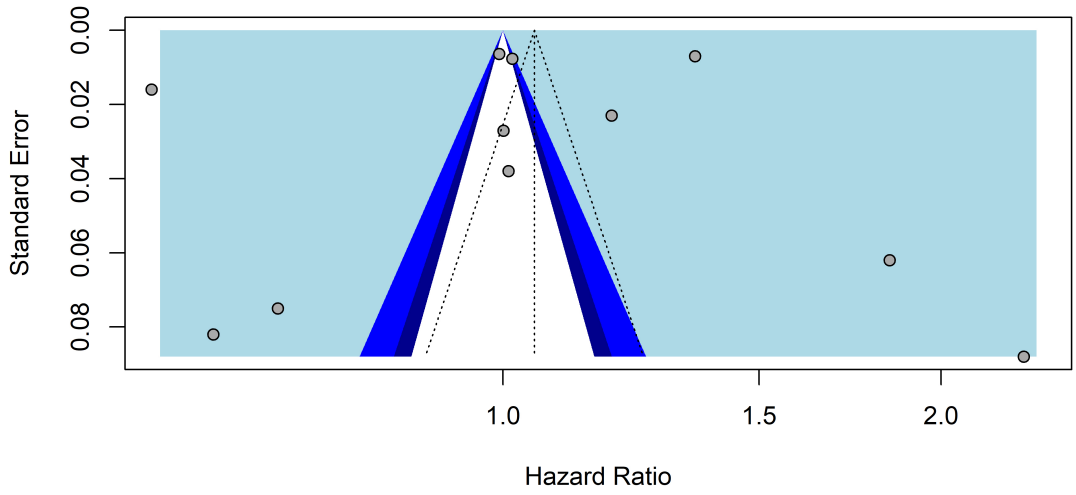

FIGURE 6. Distribution of HR with SE (logHR) in included studies.

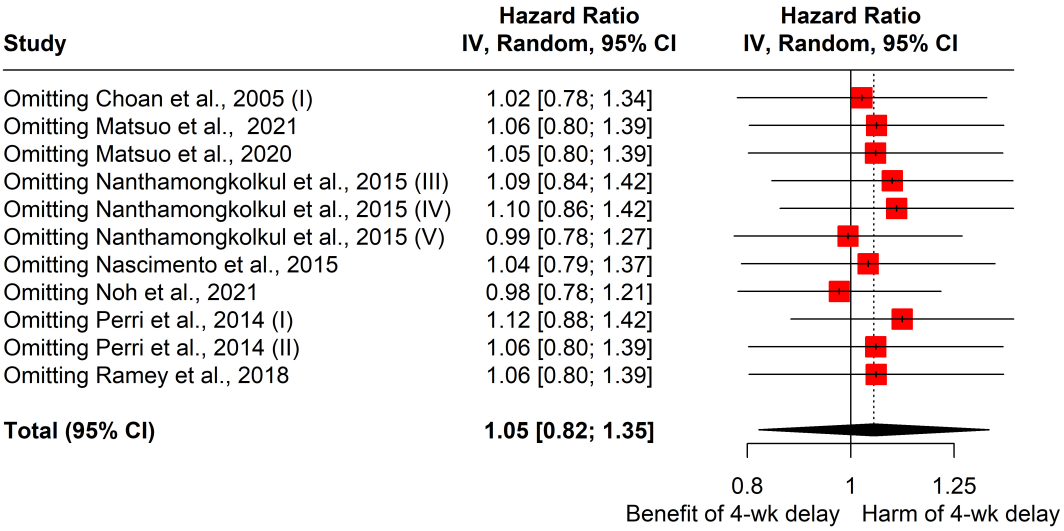

FIGURE 7. Influence analysis of included studies using a leave-one-out method. CI: Confidence Interval.

surgery was performed [32, 33], it can be observed that both the number and size of studies played a substantial role in the between-study heterogeneity (Chi squared = 150.44, *df* = 3, $p < 0.01$). This could not be the only source of variation, as the test statistic (chi squared) still fails to be powerful enough in a small number of studies [36]. There is very high between-study heterogeneity (*I* squared = 98%), suggesting unaccounted sources of variation across effects considered. Quite distinct from others, one of the comparison groups by Nanthamongkolkul (Nanthamongkolkul *et al.* [32], 2015 (V) evaluated the 8-weeks waiting time against the OS of post-five years. This, then, might overestimate the effect size compared to the other comparison groups in the subgroup. Nonetheless, there is evidence in this line that a few weeks of delay in treatment in early-stage cervical cancer has an inconclusive association with 5-year OS [37] or even 3-year OS as illustrated by two comparison groups in the last subgroup [14]. This could, possibly, be due to an improved cure rate or the very slow prognosis of the disease following management at this stage [8]. Finally, the methods employed in data analysis, assumptions, and robustness of models could be implicated in these differences. For instance, the studies by Matsuo *et al.* [30, 33] employed a cubic spline transformation with a non-linear assumption of waiting times. In some studies, methods were reported to test the proportionality of hazard assumptions, while others lacked them.

While the sources of variability described above could be regarded as potential areas for statistical heterogeneity, it still remains hard to reach a conclusion. Ideally, the tests used (though *I* squared might be less sensitive to the number of studies compared with the Q squared statistics) might yet fail to detect the precise level of variability between the true and observed effects [26]. There could also be challenges in uncovering other causes of variance ascribed to the design-level or baseline biases in individual studies. These may include the particular intervention types and dosages patients received, the possible method-driven diversities, such as the risk of bias during the recruitment process, outcome measurement, degree of loss to follow-up, or a combination of any of them. For instance, results from studies that consider a cubic spline transformation could exhibit distinct directionality compared to others'. This, in turn, poses a cumulative influence that challenges the easier interpretation of the pooled effect measure in this review.

The random effects meta-analysis strategy used in this paper is intended to handle heterogeneity in effect sizes across studies that is due to sampling error within each study. The pooled effect from a subgroup of two studies showed that a 4-week delay in radiotherapy initiation was associated with a 1.27 times higher rate of death. Extending the waiting time to 8-week or 12-week, we found that the rate of mortality increased by 1.61 (95% CI: 1.24–2.09) or 2.01 (95% CI: 1.39–3.01) respectively, compared to the non-delayed groups. The study by Dereje *et al.* [32] in a cohort of patients with similar stages of cancer and treatment types but with a 3-year follow-up period. It reported that each two-month delay of treatment can increase the rate of mortality twice as much as the group who received the treatment within the same period. The reported level of o mortality among the latter is seemingly higher because ours was based on the weighted averages of two studies over a relatively longer period of follow-up. This is in agreement with guideline recommendations that treatment options requiring radiotherapy should be started within a month [38, 39]. It is reasonable to consider that patient groups under this indication come from an advanced stage of the disease, as was also noted in the included studies. The rate of worse prognosis has been reported to be fast following the delay of treatment in patients with advanced-stage breast cancer [40] though opposing evidence exists in a report among patients with lung cancer [41]. An additional possible reason could be that the samples considered in the pooled studies were slightly younger (median: 51–52 *vs.* 55 years). Patients with advanced age may have an increased rate of mortality owing to the associated comorbidities [42].

On the contrary, no statistically significant rate of mortality was noted between the delayed and non-delayed groups under combined chemo-radiotherapy. Neither did the relatively shorter follow-up period for the same treatment reveal a significant difference. In fact, more than 86% of the patients in the studies by Noh *et al.* [13] and Matsuo *et al.* [30] were diagnosed with squamous cell carcinoma (SCC) at similar stages. Yet, the exclusion of patients with waiting times beyond 1 year in the latter study might underscore the effect of delayed treatment on survival. Longer than optimal lag times were generally reported to increase the risk of mortality in cancer cases [43]. This may contribute to the non-differential rate of mortality among these groups, given that other exposures are alike. A study also reported that patients with squamous cell carcinoma (SCC) have better OS and DFS compared to those with adenocarcinoma following chemoradiation [44]. In the study by Ramey *et al.* [12], even though most of the patients (85%) received chemoradiation therapy, the effect of delay from the expected date of initiation was reported to be lower in this group compared to those who received radiotherapy. Furthermore, the addition of chemotherapy to radiation has been reported to be effective in improving survival outcomes [45] possibly masking the effect of the disparity in waiting times in this population. Waiting time could be a main reason for disease progression. Further to this, factors, such as comorbid conditions, could contribute to the indifference in the risk of mortality, such that the group with non-delayed treatment might have been at increased risk or were experiencing more clinical symptoms. This variation, however, was not assessed, as all studies did not report on such measures. Such a paradox has been widely documented in the literature, where patients with shorter intervals between diagnosis and treatment initiation were reported to experience worse outcomes [43, 46]. Even though assessing potential confounders, such as tumor aggressiveness or cancer cell proliferation, was not possible, it is also likely that patients with symptomatic presentations were referred and treated earlier but had a poor prognosis.

In the same vein, the rate of mortality from any cause in five years among treated and delayed patients of surgery was found to be not statistically significant. One of the studies in this group showed that a waiting time of either a 4-week, 8-week, or 12-week interval had no effect on the difference in overall survival [32]. This might be plausible as the patients in this group were at an early stage of cancer (stages IA–IIB) and had

undergone radical or primary hysterectomy. Studies suggest that early-stage cervical cancer can be treated using either simple or radical hysterectomy with minimal complications [47, 48]. The five-year overall survival following radical hysterectomy was reported to reach up to 90% [48]. The interval between subsequent treatments, including neoadjuvant or adjuvant chemotherapy, has also been implicated as an additional source of bias. For example, the initiation of the next treatment before the complete recovery of patients from the first could lead to a higher risk of mortality [49]. Nonetheless, delays in cancer treatment may be differentially linked with an excess risk of cancer-related mortality [50].

A comprehensive search strategy was followed, following all necessary steps as recommended for meta-analysis of observational studies in epidemiology (MOOSE) [21], in addition to the PRISMA checklist [24] for reporting the outcomes. The result of the publication bias test in this review proved that there was no asymmetry in the included studies, detected either individually or subgroup-wise. In addition, meta-regression and subgroup analyses were considered to minimize biases originating from the waiting time paradox. These may be considered as strengths devised to avoid biases during the selection of studies. Furthermore, sensitivity analysis did not show any significant direction changes in the confidence interval of the effect measure; hence no removal of influential studies was considered in the last model. The review, however, is not without limitations. Firstly, a considerable level of heterogeneity was apparent in the meta-analysis, which might have posed a challenge in the interpretation of the findings. Secondly, despite the fact that subgrouping has been a recommendation when justified variability exists based on predefined attributes, its use in studies like the one we employed for the DFS is discouraged. Third, this review did not present an evaluation of the certainty of the evidence generated. Fourth, the exclusion of articles with no English abstract in the review might have introduced an English-language bias. Finally, the included studies lacked essential and clearly stratified patient-level data. This may include clinical symptoms, a real-time observation period, the specific type and sequence of treatment patients received, and the proportionality of hazards' assumption.

5. Conclusions

Four-week delays in initiation of radiotherapy in patients with cervical cancer resulted in an increased rate of mortality from any cause. However, there is inconclusive evidence on the association between a 4-week delay in the initiation of either surgery (hysterectomy) or chemoradiotherapy and overall survival. This might be confounded, partially, by the waiting time paradox bias. Similarly, a 4-week or more delay in surgery may not change the hazard of DFS events relative to a less than 4-week delay in surgery. It is recommended that future reviews utilize individual patient data (IPD), concentrate on researches with prospective designs when appropriate, and utilize techniques to evaluate the fundamental assumptions of the studies that are included. Additionally, based on clinically relevant stratification—such as stage, pathologic type, geographic region, age, and particular therapy types—present the dangers associated with prolonged waiting times.

AVAILABILITY OF DATA AND MATERIALS

All relevant data are within the manuscript and its supplementary files.

AUTHOR CONTRIBUTIONS

TS—was involved in conceptualization, design, data extraction, quality assurance and draft and final manuscript writing. BG—was involved in data extraction, validation and final manuscript write-up. TGF—was involved in conceptualization, supervision, validation, and editing of the draft manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This systematic review is recorded in the International Register of Systematic Review Protocols (PROSPERO) under the registration number CRD42022299689. A review protocol has been formulated and published. The review adheres to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) format in its conduct and reporting. Ethical approval was not obtained since this study involves a systematic review and meta-analysis of previously published literature.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1801482595405316096/attachment/Supplementary%20material.zip.

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