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SYSTEMATIC REVIEW

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The overtreatment rate, medical cost and psychological affection of see-and-treat versus three-step approaches in the treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis

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Abstract

Objectives The see-and-treat (S&T) approach is increasingly utilized for the treatment of cervical intraepithelial neoplasia (CIN). However, its recognition remains limited compared to the traditional three-step management. This study aims to systematically review and compare the outcomes of studies that directly assess the S&T and three-step approaches in CIN treatment.

Methods A comprehensive literature search was conducted in MEDLINE, EMBASE, and the Cochrane Library up to December 10, 2024. Eligible studies directly compared the overtreatment rate, medical costs, and psychological impact of the S&T and three-step approaches for abnormal cervical smears. The inclusion criteria for women undergoing S&T had to align with those for three-step management. Data on overtreatment risk, medical costs, and psychological effects were extracted and analyzed. Comparative results were presented using forest plots, stratified by different smear categories.

Results Twelve publications were included, comprising three randomized controlled trials (RCTs) and nine observational studies. Among women with ASC-H or HSIL, the overtreatment risk following S&T was comparable to that of the three-step approach (ASC-H, RR 1.40, 95% CI 0.75–2.60; HSIL, RR 0.93, 95% CI 0.71–1.23). However, in the LSIL/ASCUS subgroup, the S&T approach was associated with a significantly higher overtreatment risk compared to the three-step method (RR 2.03, 95% CI 1.92–2.15). The S&T approach was associated with lower medical expenses for HSIL cases and a reduction in patients' negative emotional responses compared to the three-step procedure.

Conclusions The S&T approach may be a suitable alternative for women with HSIL/ASC-H smear results, considering its comparable overtreatment risk, potential cost savings, and psychological benefits. However, its use in LSIL/ASC-US cases should be carefully evaluated due to the increased risk of overtreatment.

Keywords See-and-treat, Three-step, CIN, Overtreatment, Medical cost, Psychological affection, Systematic review

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Introduction

Cervical cancer is the fourth most common malignancy among women worldwide [1]. According to the World Health Organization (WHO), an estimated 604,000 new cases and 342,000 cancer-related deaths occurred globally in 2020 [2]. The progression of cervical cancer typically occurs over several years, advancing from cervical intraepithelial neoplasia (CIN) to invasive carcinoma. Consequently, effective and accessible cervical cancer screening is crucial in reducing both incidence and mortality [3]. The conventional three-step approach to cervical cancer screening consists of cervical cytology or HPV testing, followed by colposcopy and subsequent histopathological confirmation. This multi-step process requires multiple hospital visits, prolonging the treatment timeline and increasing the financial burden on patients [4]. Furthermore, non-adherence to follow-up appointments may lead to delayed diagnoses, thereby elevating the risk of disease progression and mortality [5, 6]. Additionally, the limited concordance between colposcopic biopsy results and the final histology of excised lesions contributes to overtreatment, with reported rates ranging from 11 to 35% [7].

The see-and-treat (S&T) approach streamlines the screening and treatment process by enabling Loop Electrosurgical Excision Procedure (LEEP) to be performed immediately after an abnormal cervical smear result, thereby reducing the number of hospital visits and shortening the treatment interval [8, 9]. However, the omission of colposcopic biopsy in this approach raises concerns regarding potential overtreatment, which may result in unnecessary complications such as vaginal bleeding, excessive discharge, and long-term reproductive issues, including an increased risk of miscarriage and preterm birth [6, 10–13].

Although several studies have compared the S&T and three-step approaches, gaps in the literature remain concerning their relative effectiveness, particularly in overtreatment risk, cost-effectiveness, and psychological impact. This review aims to address these gaps by providing a comprehensive comparison of the overtreatment rates, medical costs, and psychological effects of the S&T and three-step approaches. By focusing exclusively on studies that directly compare these two protocols in patients eligible for either procedure, this review seeks to offer a more reliable and nuanced assessment of their respective advantages and limitations.

Methods

Data sources and search

A comprehensive search was conducted across MEDLINE, EMBASE, and the Cochrane Library from inception to December 10, 2024, to identify studies comparing the S&T approach with the three-step approach for women suspected of having CIN. The search strategy employed a combination of terms related to S&T management, CIN, three-step approach, and LEEP (Box S1). Additionally, manual searches of reference lists and relevant articles were performed. Duplicate entries were removed using the bibliographic software EndNote X5. (Thomas Reuters, New York City, NY, USA).

Studies were eligible for inclusion if the following criteria were fulfilled: (1) Reporting of a preceding cervical smear. (2) All participants must undergo one of the two screening-treatment protocols: the 'see-and-treat' approach, in which LEEP is performed directly after an abnormal cervical cytology result, or the 'three-step' approach, in which an excisional procedure is performed only after colposcopic biopsy confirms CIN2 or worse. (3) Reporting of histopathological outcomes from cervical biopsy and excision, classified as low-grade (no CIN or CIN1) or high-grade (CIN2 or worse). (4) Direct comparability of the S&T and three-step treatment groups, ensuring that lesions treated with S&T would have been eligible for the three-step approach. (5) Reporting of at least one key outcome measure: overtreatment rate, medical costs, or psychological impact. Two reviewers independently assessed study eligibility, resolving discrepancies through discussion with a third reviewer.

Data extraction

For each included study, the following data were extracted and recorded in Microsoft Excel: author and publication year, study location and period, study design (RCT, cross-sectional, cohort), case definition and treatment approach, number of participants, criteria for overtreatment, associated medical costs, and psychological impact on patients. The primary outcome was the comparison of overtreatment rates, defined as CIN1 or less in the final excision specimen histopathology. Secondary outcomes included comparisons of medical costs and the psychological impact of each approach.

The systematic review was registered in PROSPERO (CRD42024574810). Study quality was assessed using the Agency for Healthcare Research and Quality (AHRQ) tool, categorizing studies as low, medium, or high risk of bias based on a 15-item quality assessment checklist (Figure S1).

Statistical analysis

Study results were stratified based on cervical smear findings into three subgroups: (1) High-grade squamous intraepithelial lesion (HSIL); (2) Atypical squamous cells, cannot exclude HSIL (ASC-H); (3) Low-grade intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance (ASC-US). Data synthesis utilized

the inverse variance method to calculate pooled incidences and 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 test and categorized as follows: low heterogeneity ($I^2 < 25\%$), moderate heterogeneity ($I^2 = 25\% - 50\%$), and high heterogeneity ($I^2 > 50\%$). A random-effects model was applied for analyses exhibiting moderate to high heterogeneity, while a fixed-effects model was used when heterogeneity was low. Zero-cell counts were adjusted by adding a fixed value of 0.5 to all table cells for standard error calculations. Sensitivity analyses were conducted to examine the influence of individual studies on overtreatment rates by sequentially excluding: Loopik et al. (the largest study), Chigbu et al. (small study) and Guducu et al. (small study) [14–16]. All statistical analyses were performed using Review Manager 5.0 (Cochrane Collaboration, Copenhagen) and results were reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results

A total of 1,529 publications were identified (Fig. 1), of which 61 were deemed potentially eligible. After removing 510 duplicate studies and excluding 953 studies that were irrelevant to the research focus, a full-text review was conducted on the remaining articles. An additional 49 studies were excluded for the following reasons: 27 studies did not directly compare the S&T and three-step approaches, 8 studies evaluated colposcopic appearances between abnormal cervical smears and LEEP, 8 studies did not classify the cervical smear results into HSIL, ASC-H, LSIL/ASC-US, and 6 studies did not

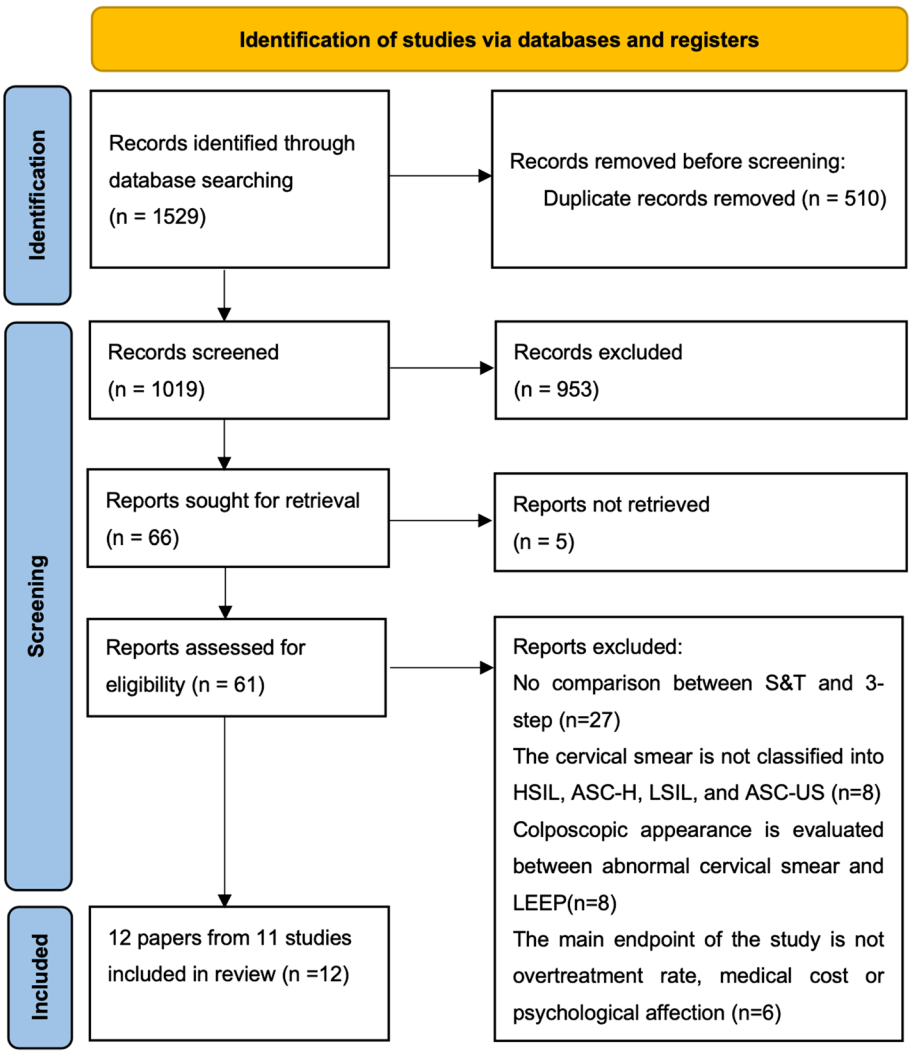

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process

assess overtreatment rates, medical costs, or psychological impact. Ultimately, 12 articles representing 11 studies met the inclusion criteria, comprising 22,550 patients with abnormal cervical cytology (Table 1) [14–25]. Among them, nine articles included women with HSIL cytology, six included LSIL/ASC-US, and two studies included ASC-H. The overall study quality assessment is presented in Figure S1.

Risk of overtreatment

Among women with HSIL (n = 13,785), 5,476 underwent the S&T procedure across eight studies, with 659 (12.0%) classified as overtreated. The overtreatment risk in HSIL cytology was lower with S&T than with the three-step approach (12.0% vs. 14.3%); however, this difference was not statistically significant (risk ratio, RR 0.93, 95% CI 0.71–1.23, Fig. 2). For women with ASC-H (n = 389), the S&T group exhibited a higher overtreatment rate than the three-step group (24.2% vs. 18.9%), though this difference was also not statistically significant (RR 1.40, 95% CI 0.75–2.60, Fig. 3). In four studies including women with LSIL/ASC-US (n = 6,166), 1,560 of 2,362 women (66.0%) in the S&T group were classified as overtreated. The risk of overtreatment was significantly higher in the S&T approach compared to the three-step approach (RR 2.03, 95% CI 1.92–2.15, Fig. 4). Sensitivity analyses, including the exclusion of small studies and the largest study by Loopik et al., did not significantly alter the results.

Table 1 Characteristics of the included studies

Author	Year	Country	Study Type	Total number of patients	"See-and-treat" patients	"Three-step" patients	Referral cervical smear	Endpoint
Sadan et al	2005	Israel	Observational study	144	81	63	HSIL	Overtreatment rate
Cho et al	2009	Korea	Observational study	829	432	397	HSIL/LSIL + ASCUS	Overtreatment rate
Balasubramani et al	2006	UK	Observational study	272	136	136	HSIL	Psychological states
TOMBOLA Group	2009	UK	Randomized controlled trials	1982	982	1000	LSIL	Medical cost
Sharp et al	2010	UK	Randomized controlled trials	989	487	502	LSIL	Psychological states
Chigbu et al	2013	Nigeria	Randomized controlled trials	314	157	157	HSIL	Overtreatment rate; Medical cost
Guducu et al	2013	Turkey	Observational study	116	55	61	HSIL/ASCUS-H/LSIL + ASCUS	Overtreatment rate
Meirovitz et al	2014	Israel	Observational study	403	72	331	HSIL	Overtreatment rate
Aksan-Desteli et al	2014	Turkey	Observational study	176	38	32	ASCUS/LSIL	Overtreatment rate
Kuroki et al	2016	US	Observational study	178	86	92	HSIL	Overtreatment rate
Loopik et al	2020	Netherland	Observational study	17,564	6851	10,713	HSIL/LSIL + ASCUS	Overtreatment rate
Kiviharju et al	2022	Finland	Observational study	572	360	212	HSIL/ASCUS-H	Overtreatment rate

HSIL high-grade squamous intraepithelial lesion, *LSIL* low-grade intraepithelial lesion, *ASC-H* atypical squamous cells, cannot exclude HSIL, *ASC-US* atypical squamous cells of undetermined significance

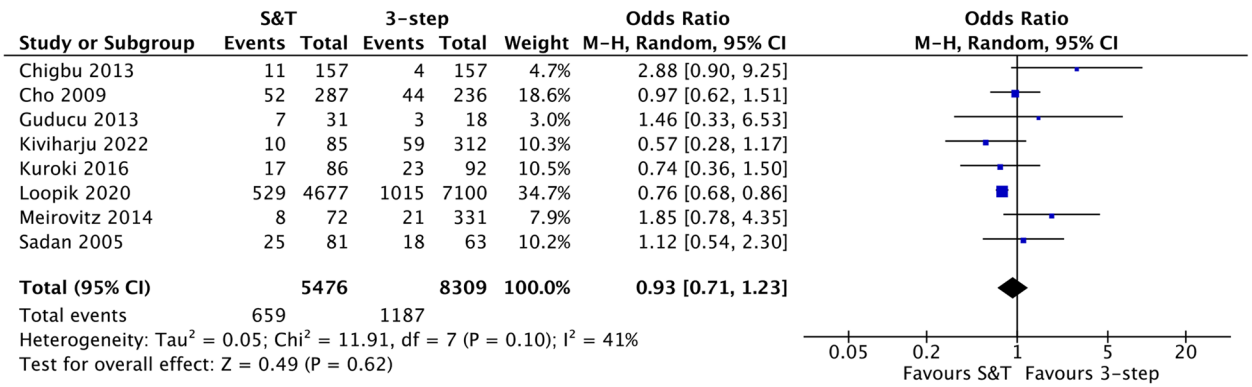

Fig. 2 Forest plot of overtreatment rate in studies with HSIL cervical smear

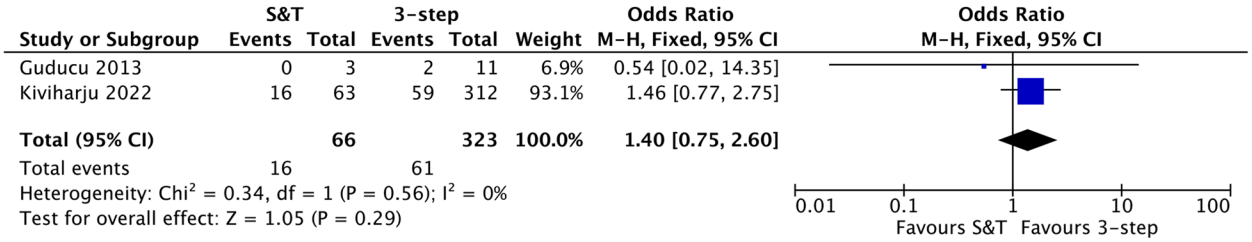

Fig. 3 Forest plot of overtreatment rate in studies with ASC-H cervical smear

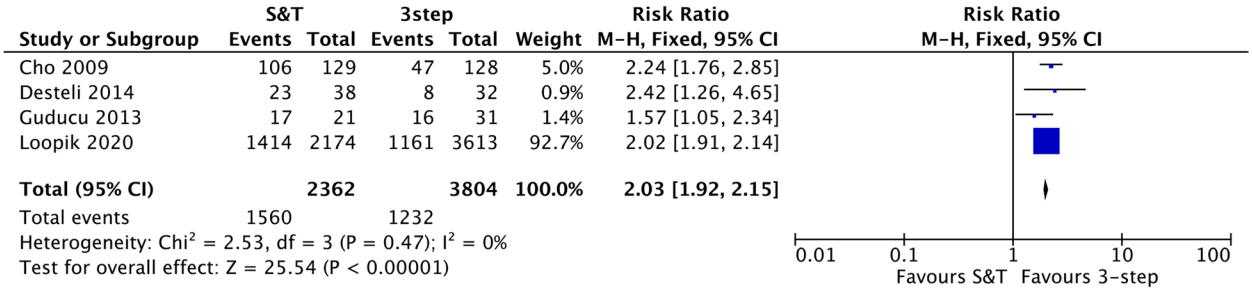

Fig. 4 Forest plot of overtreatment rate in studies with LSIL/ASC-US cervical smear

Medical costs

The TOMBOLA group(2009) [22] examined the cost-effectiveness of cytological surveillance, S&T, and the three-step approach in patients with LSIL cytology, considering both direct (health care) and indirect (time and travel) costs. The study found no significant differences in the cost-effectiveness ratios among the three approaches.

In contrast, Chigbu et al. [14] conducted a cost comparison between the S&T and three-step protocols in HSIL patients. The three-step protocol incurred additional costs for colposcopic biopsy, biopsy histology, LEEP, and LEEP histology, whereas the S&T protocol only included LEEP and LEEP histology. The results demonstrated that S&T was significantly more cost-effective, primarily due to the elimination of colposcopic biopsy step.

Psychological affection

Balasubramani et al. [23, 26] assessed the psychological impact of the S&T and three-step approaches in HSIL patients using the Spielberger State-Trait Anxiety Inventory (STAI). Anxiety levels were measured seven days after the initial colposcopy appointment, revealing that women in the S&T group experienced significantly lower anxiety levels and a greater sense of relief compared to those in the three-step group.

Sharp et al. [27] evaluated the long-term psychological effects of both approaches in LSIL patients, utilizing the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale (IES) at 6 weeks, 12, 18, 24, and 30 months post-procedure. The study found no significant differences between the two groups in terms of depression (OR = 0.78, 95% CI 0.52–1.17) or anxiety (OR = 0.83, 95% CI 0.57–1.19).

Discussion

This systematic review suggests that for women with HSIL/ASC-H smears, the overtreatment risk of S&T approach may be comparable to that of the three-step approach, though findings are primarily based on observational data and limited RCTs. Conversely, for women with LSIL/ASC-US smears, the three-step approach appears to carry a significantly lower overtreatment risk than the S&T approach. Additionally, the S&T approach may offer economic advantages for HSIL patients, while no significant cost differences were observed for LSIL patients. Moreover, the S&T approach appears to be more effective in reducing psychological distress in HSIL patients compared to the three-step approach.

Earlier reviews on S&T overtreatment rates analyzed individual treatment types [7, 28], with studies including colposcopic impression as an additional step. This resulted in an overall overtreatment rate of 11.6% (95% CI 7.8–15.3%) for high-grade cytology with high-grade colposcopic impressions. While colposcopic impression enhances diagnostic accuracy, it is subjective and expertise-dependent, limiting its broader applicability [29]. Our findings suggest that for HSIL/ASC-H patients, proceeding with S&T without colposcopic impression does not increase overtreatment risk, supporting its promotion, particularly in resource-limited settings.

Colposcopically guided biopsies also require expertise, and random or routine site biopsies may miss the most severe lesion, leading to underdiagnosis. A multicenter study in Denmark ($n = 102$, aged ≥ 45) found that CIN2 + detection rates in LEEP specimens were significantly higher than in biopsies, emphasizing the risk of underdiagnosis when relying solely on biopsies [30]. Thus, for HSIL/ASC-H patients, the S&T protocol achieves a balance between minimizing overtreatment and reducing the risk of underdiagnosis. Conversely, for ASC-US/LSIL patients, the S&T approach significantly increases overtreatment risk. Given that many low-grade lesions regress spontaneously, the three-step approach allows for lesion evaluation over time [31], reducing unnecessary interventions and associated risks (e.g., cervical stenosis, preterm birth) [32–35]. These findings highlight the need to balance risks and benefits, with three-step management being preferable for ASC-US/LSIL patients.

Comparative cost-effectiveness data on S&T versus three-step protocols are scarce. Discrepancies between the TOMBOLA study (UK) and Chigbu's study (Nigeria) highlight the impact of healthcare financing and disease severity. In the UK's National Health Service (NHS), universal healthcare likely minimizes cost differences between treatment strategies, particularly for LSIL patients, where immediate treatment is often unnecessary. Conversely, in Nigeria's out-of-pocket healthcare system, cost is a critical factor, and eliminating colposcopic biopsy in HSIL patients significantly reduces expenses. These differences underscore the importance of considering economic contexts when evaluating cost-effectiveness. Future studies should explore cost-effectiveness across different healthcare financing models. A 2016 Markov model by Nghiem et al. found that S&T is cost-effective only when adherence to standard care is high and the disutility of LEEP is low [36]. Cost savings from reduced biopsies were offset by expenses from additional LEEP procedures, reinforcing that S&T is economically viable only when overtreatment rates are minimized. As the S&T does not increase the overtreatment rate in HSIL/ASC-H subgroup, it appears to be a suitable option in resource-limited settings based on the limited evidence.

Psychological impact comparisons remain limited. Previous studies have shown that colposcopy can induce psychological distress, with patients diagnosed with CIN2 + experiencing higher anxiety levels than those with lower-grade lesions [37, 38]. Balasubramani et al. assessed short-term anxiety (7 days post-colposcopy) using the STAI and found lower anxiety in the S&T group, likely due to immediate resolution of uncertainty. In contrast, Sharp et al., using HADS and IES for long-term psychological assessment (up to 30 months) found no significant differences, suggesting that distress diminishes over time regardless approach. Differences in patient populations may also contribute—Balasubramani et al. focused on HSIL patients (higher initial anxiety), while Sharp et al. studied LSIL patients (lower initial distress). Further longitudinal studies utilizing standardized psychological assessment tools at multiple time points are needed to better understand the psychological impact of different treatment approaches and optimize mental health support.

To our knowledge, this is the first systematic review directly comparing the S&T and three-step approaches for the management of abnormal cervical cytology. The inclusion of studies with consistent eligibility criteria, along with a large sample size ($n = 22{,}550$), strengthens the reliability of the findings. However, several limitations must be acknowledged. First, the strict inclusion criteria led to a limited number of eligible studies. Notably, only two RCTs were included in the overtreatment comparison, while the remaining nine were cohort or retrospective case–control studies. The predominance of observational studies introduces potential biases, such as selection and confounding bias, affecting the reliability of findings. Future research should prioritize well-designed RCTs to strengthen evidence on the effectiveness of S&T versus three-step approaches. Second, although studies applied consistent eligibility criteria, variations in patient characteristics (e.g., age, race, and healthcare practices) may introduce heterogeneity that could influence treatment outcomes. Third, variability in psychological assessment tools and differences in cost-effectiveness analyses across healthcare systems limit the generalizability of the findings and preclude the possibility of conducting a meta-analysis. Consequently, the results were synthesized narratively rather than quantitatively. Standardized assessment methodologies and larger RCTs are necessary to further validate the clinical utility of the S&T approach.

Our findings indicate that the S&T approach may serve as an effective and efficient strategy for managing HSIL/ASC-H patients, particularly in resource-limited settings. However, given the reliance on observational studies and the variability in clinical practices, these conclusions should be interpreted with caution. Future RCTs could refine patient selection criteria and providing more robust evidence. Additionally, the integration of HPV genotyping and novel biomarkers may further reduce overtreatment rates, ultimately improving patient outcomes.

Conclusion

This review suggests that the S&T approach may be a feasible management strategy for HSIL/ASC-H patients, with overtreatment rates that appear comparable to the three-step approach in some studies. Additionally, for HSIL cases, S&T may offer economic benefits. However, for LSIL/ASC-US patients, the increased risk of overtreatment with S&T warrants cautious evaluation, and treatment decisions should prioritize clinical considerations over cost-effectiveness. Given the predominance of observational data and healthcare system variability, further high-quality RCTs are needed to confirm the long-term efficacy, safety, and cost-effectiveness of the S&T approach.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-025-03718-y.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Authors' contributions

Shuwen Zhang: Conceptualization, Data Curation, Methodology, Software, Investigation, Formal Analysis, Writing—Original Draft; Lan Zhu: Visualization, Investigation, Validation, Resources, Supervision, Project Administration; Jinhui Wang: Conceptualization, Funding Acquisition, Resources, Visualization, Supervision, Writing—Review & Editing; All authors: Approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Data availability

Data sharing is not applicable as no new data were generated. The data used in this paper were obtained from previously published research.

Declarations

Ethics approval and consent to participate

No ethics approval was needed, as the current study is a systematic review based on previously published data.

Competing interests

The authors declare no competing interests.

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