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REVIEW ARTICLE

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A systematic review and meta-analysis of thermal coagulation compared with cryotherapy to treat precancerous cervical lesions in low- and middle-income countries

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Abstract

Background: Thermal coagulation is gaining popularity for treating cervical intraepithelial neoplasia (CIN) in screening programs in low- and middle-income countries (LMICs) due to unavailability of cryotherapy.

Objectives: Assess the effectiveness of thermal coagulation for treatment of CIN lesions compared with cryotherapy, with a focus on LMICs.

Search strategy: Papers were identified from previous reviews and electronic literature search in February 2018 with publication date after 2010.

Selection criteria: Publications with original data evaluating cryotherapy or thermal coagulation with proportion of cure as outcome, assessed by colposcopy, biopsy, cytology, and/or visual inspection with acetic acid (VIA), and minimum 6 months follow-up.

Data collection and analysis: Pooled proportions of cure are presented stratified per treatment modality, type of lesion, and region.

Main results: Pooled cure proportions for cryotherapy and thermal coagulation, respectively, were 93.8% (95% CI, 88.5–97.7) and 91.4% (95% CI, 84.9–96.4) for CIN 1; 82.6% (95% CI, 77.4–87.3) and 91.6% (95% CI, 88.2–94.5) for CIN 2–3; and 92.8% (95% CI, 85.6–97.7) and 90.1% (95% CI, 87.0–92.8) for VIA-positive lesions. For thermal coagulation of CIN 2–3 lesions in LMICs 82.4% (95% CI, 75.4–88.6).

Conclusions: Both cryotherapy and thermal coagulation are effective treatment modalities for CIN lesions in LMICs.

KEYWORDS

Cervical cancer screening; Cervical intraepithelial neoplasia; Cryotherapy; Effectiveness; Low- and middle-income countries; Systematic review; Thermal coagulation

1 | INTRODUCTION

Thermal coagulation is gaining popularity for treating cervical intraepithelial neoplasia (CIN) in cervical cancer screening programs in low- and middle-income countries (LMICs) due to unavailability of gas and high maintenance for cryotherapy.

Cervical cancer is one of the leading cancers among women worldwide, with an estimated 570 000 new cases and 311 000 deaths

each year.[1] The burden of cervical cancer disproportionately affects LMICs, where 85% of cases occur.[1] Screening programs aim to prevent cervical cancer by more than 85% of cases timely treatment of precancerous cervical lesions. In resource-constrained settings, the WHO recommends see-and-treat screening programs where women are screened and treated in a single visit with the loop-electrosurgical excision procedure (LEEP) or cryotherapy.[2]

The number of LMICs with national screening programs has increased over the years, but coverage remains low.[3] There are numerous factors influencing uptake of screening programs, including lack of skilled healthcare workers, lack of equipment, and other health system challenges. An important logistical constraint for the sustainability of see-and-treat programs is maintenance of cryotherapy devices and the lack of availability of refrigerated gas, owing to its high importation and purchase costs and large-size cylinders needed for transport to treatment sites.[4,5] This affects the availability of treatment during screening, and thus the success of screen-and-treat programs.

Thermal coagulation is an alternative ablative technique using electricity to destroy the premalignant cervical lesions by heating. The device is small and lightweight, making it practical for use in an outpatient setting with minimal complications. These advantages are particularly important in rural and outreach settings.[4,5]

In 2013 and 2014, Sauvaget et al.[6] and Dolman et al.[7] published separate meta-analyses analyzing the efficacy of cryotherapy and thermal coagulation to treat CIN lesions in mainly high-income countries, demonstrating cure proportions of 94.0% (CIN 1), 92.0% (CIN 2), and 85.0% (CIN 3) for cryotherapy, and 96% (CIN 1) and 95% (CIN 2–3) for thermal coagulation. However, data from LMICs included in previous meta-analyses of thermal coagulation were limited to one paper from Singaporeand one from India.[8,9] To assess the efficacy of thermal coagulation in LMICs, more data from these settings should be reviewed. LMICs differ from high-income countries in terms of healthcare structures and patient population, therefore efficacy may not be equal; for example, HIV-positivity rates are higher in LMICs than in Europe and Northern America, consequently with higher prevalence and recurrence of CIN lesions.[2]

The aim of the present systematic review and meta-analysis was to assess the effectiveness of thermal coagulation to treat CIN lesions compared with cryotherapy, with focus on LMICs.

2 | MATERIALS AND METHODS

Papers were identified using two strategies: (1) identified papers from the previous meta-analyses,[6,7] which included papers until 2011 and 2013, respectively, were reviewed according to the inclusion and exclusion criteria described below; and (2) an electronic literature search was conducted to identify new relevant papers published after 2010.

2.1 | Search strategy

An electronic literature search (February 2018) was performed in PubMed, Embase, Web of Science, Cochrane Library, regional databases, and Google Scholar with assistance from a medical librarian. A wide range of definitions are used in the literature, therefore different keywords were included to cover all related publications (Data S1). Papers with a publication date before 2010 were excluded to avoid overlap with the existing meta-analyses. In Google Scholar, no date limitation was used because this database had not been searched in the meta-analyses of Sauvaget et al.[6] and Dolman et al.[7]

2.2 | Eligibility criteria

Titles and abstracts of all papers were reviewed by three researchers (MF, AR, RO) for relevance and presence of original data. The remaining papers were reviewed by three researchers (AR, RO, MF) and retained if the following criteria were met: cure proportion was the outcome measure and was defined by colposcopy, biopsy, cytology, and/or visual inspection with acetic acid (VIA)/visual inspection with Lugol iodine (VILI). Cytology and pathology are not always available to measure treatment outcome in LMICs; instead, screening is frequently performed by VIA or VILI. As such, papers defining cure proportion with VIA- or VILI technique were considered.

Papers not based on original data or with insufficient data on cure proportion and follow-up were excluded. Follow-up duration had to be 6 months or more after initial treatment, sample size more than 25 patients, and loss of patients attending follow-up not more than 50%. Cryotherapy for CIN 2–3 had to be provided with the double-freeze method, and the treatment procedure had to be performed for no other reason than for treating CIN, nor be provided simultaneously with other treatment. In case of discordant results, consensus was reached among four researchers (AR, RO, MF, JB).

2.3 | Risk of bias assessment

Study quality was assessed using a component approach.[10] Unknown HIV status of screening participants and loss to follow-up of greater than 25% were considered high risk of bias. Studies using cytology or histology to assess outcome were considered low risk of bias compared with VIA-based outcomes. The eligibility criteria described above aimed to eliminate studies with very poor study quality.

2.4 | Data extraction

For all relevant identified papers, a data extraction sheet was completed in Excel (Microsoft; Richmond, WA, USA). All extracted data were verified independently by two researchers (MF and AM or RO). The following items were collected: author; year of publication; country; study year; study setting; study design; age of patients; case definition (CIN grade or VIA/VILI); case confirmed by biopsy; endocervical involvement; HIV status of patients; treatment provider; treatment procedure (single/double freeze for cryotherapy; temperature, duration, and number of applications for thermal coagulation); number of patients treated; number of patients attending follow-up; number of patients cured; follow-up duration; definition of cure (negative VIA/VILI, cytology, colposcopy, or

biopsy); single visit see-and-treat approach; pain; adverse effects; and fertility outcome. Cure rates were defined as a proportion with the number of women with negative VIA/VILI, negative cytology, negative colposcopy, or negative biopsy at a minimum of 6 months' follow-up duration divided by the number of women attending follow-up. Therefore, the terminology "proportion cured" or "cure proportion" was used instead of "cure rate".

2.5 | Statistical analysis

Pooled cure proportions with 95% confidence intervals were the primary outcome. Cure proportions were pooled in a random effects model. Analyses were stratified by treatment modality (cryotherapy versus thermal coagulation). If both 6- and 12-months' follow-up data were available, 12-months' follow-up data were used as this is the recommended follow-up duration for detection of persistent disease after initial treatment.[2] Studies were stratified per CIN grade (CIN 1, CIN 2–3, or VIA/VILI outcome) and region (Europe, North America, South America, Africa, and Asia). In a sensitivity analysis, the effect of follow-up attendance on cure rates was assessed comparing studies with 50%–75% and more than 75% follow-up attendance.

The degree of heterogeneity among studies was assessed by calculating I^2 statistic values: 0%–25% represented mild heterogeneity, 25%–50% moderate heterogeneity, and more than 50% large heterogeneity. Publication bias was assessed by means of visual assessment plotting cure proportions against sample size. Because the number of studies was small, testing on publication bias was not indicated. Forest plots were created using STATA version 14.0 (Stata Corp LLP, College Station, TX, USA).

3 | RESULTS

3.1 | Papers identified via literature search

The electronic search yielded a total of 445 unique references from PubMed (n=154), Embase (n=111), Web of Science (n=21), Cochrane Library (n=0), regional databases (n=129), and Google Scholar (n=30). An additional search in clinical trial registers and journal databases yielded no additional publications.

After reviewing the title and abstract of all papers, 28 relevant papers were identified on cryotherapy and 20 on thermal coagulation. After full-text review, 11 papers on cryotherapy and seven on thermal coagulation were eligible for inclusion.

Since publication of the meta-analysis by Sauvaget et al.,[6] no new papers on cryotherapy from North America or Europe have been published, therefore these regions were excluded from further analysis for cryotherapy.

3.2 | Papers from previous meta-analyses

Sauvaget et al.[6] included 20 studies from Asia, Africa, or South America in their meta-analysis on cryotherapy. In the present review, five of these studies were excluded owing to sample size of less than 25 patients, recurrence not specified per CIN grade, single-freeze technique for CIN 2–3 lesions, or no original data.[11–15] The remaining 15 studies conducted in Africa (n=5), Asia (n=7), and South America (n=3) were included in the present review.

Dolman et al.[7] included 13 studies in their meta-analysis on thermal coagulation. For the present review, five of these studies were excluded owing to follow-up duration of less than 6 months, insufficient data to calculate cure rates, and cure rates not differentiated per CIN grade.[16–20] The remaining eight studies conducted in Asia (n=2), North America (n=1), and Europe (n=5) were included in the present review.

Figure 1 provides an overview of the included papers from the literature search and previous meta-analyses. Table 1 provides the details and references of the 40 included papers.[8,9,14,21–58] An overview of the excluded studies is provided as Table S1.[11–20]

3.3 | Data from included papers

In total, data from 26 studies of 14 355 patients treated with cryotherapy and 15 studies of 4864 patients treated with thermal coagulation were included. Most papers were published in the last 10 years and described treatment by cryotherapy. Table 2 provides a summary of the papers. The distribution of patients with CIN 1, CIN 2–3, and VIA-positive lesions between studies on cryotherapy and thermal coagulation was unequal. Most papers on cryotherapy treated patients with CIN 1 lesions, whereas most papers on thermal coagulation treated patients with CIN 2–3 lesions. Follow-up attendance was similar; however, studies using the VIA-approach had lower follow-up attendance compared with studies with biopsy- or cytology-based follow-up methods.

3.4 | Risk of bias assessment

Of the 26 included papers on cryotherapy, 6 (23%) provided data on the HIV status of participants. Twenty (77%) papers reported a follow-up attendance of more than 75%. Tai et al.[45] defined cure at follow-up as absence of CIN 3 lesions and did not include recurrence or persistence of CIN 1 and CIN 2 lesions. Of the 15 included papers on thermal coagulation, HIV status was reported for 3 (20%) papers. Eleven (73%) papers had a follow-up attendance of more than 75%. Visual assessment of cure rates in order of sample size did not suggest publication bias.

3.5 | Efficacy of treating CIN lesions

Figure 2 and Tables S2 and S3 demonstrate the pooled cure proportions for cryotherapy in LMICs: 93.8% (95% CI, 88.5–97.7) for CIN 1, 82.6% (95% CI, 77.4–87.3) for CIN 2–3, and 92.8% (95% CI, 85.6–97.7) for VIA-positive lesions. Figure 3 and Tables S4 and S5 show the pooled cure proportions for thermal coagulation: 91.4% (95% CI, 84.9–96.4) for CIN 1, 91.6% (95% CI, 88.2–94.5) for CIN 2–3, and 90.1% (95% CI, 87.0–92.8) for VIA-positive lesions. The pooled cure proportion for thermal coagulation in LMICs only was 82.4% (95% CI, 75.4–88.6) for CIN 2–3 lesions (Table S6).

Sensitivity analysis showed higher proportions of cure for cryotherapy papers with follow-up attendance of more than 75% for both CIN 1 and CIN 2–3 lesions (Table S7).

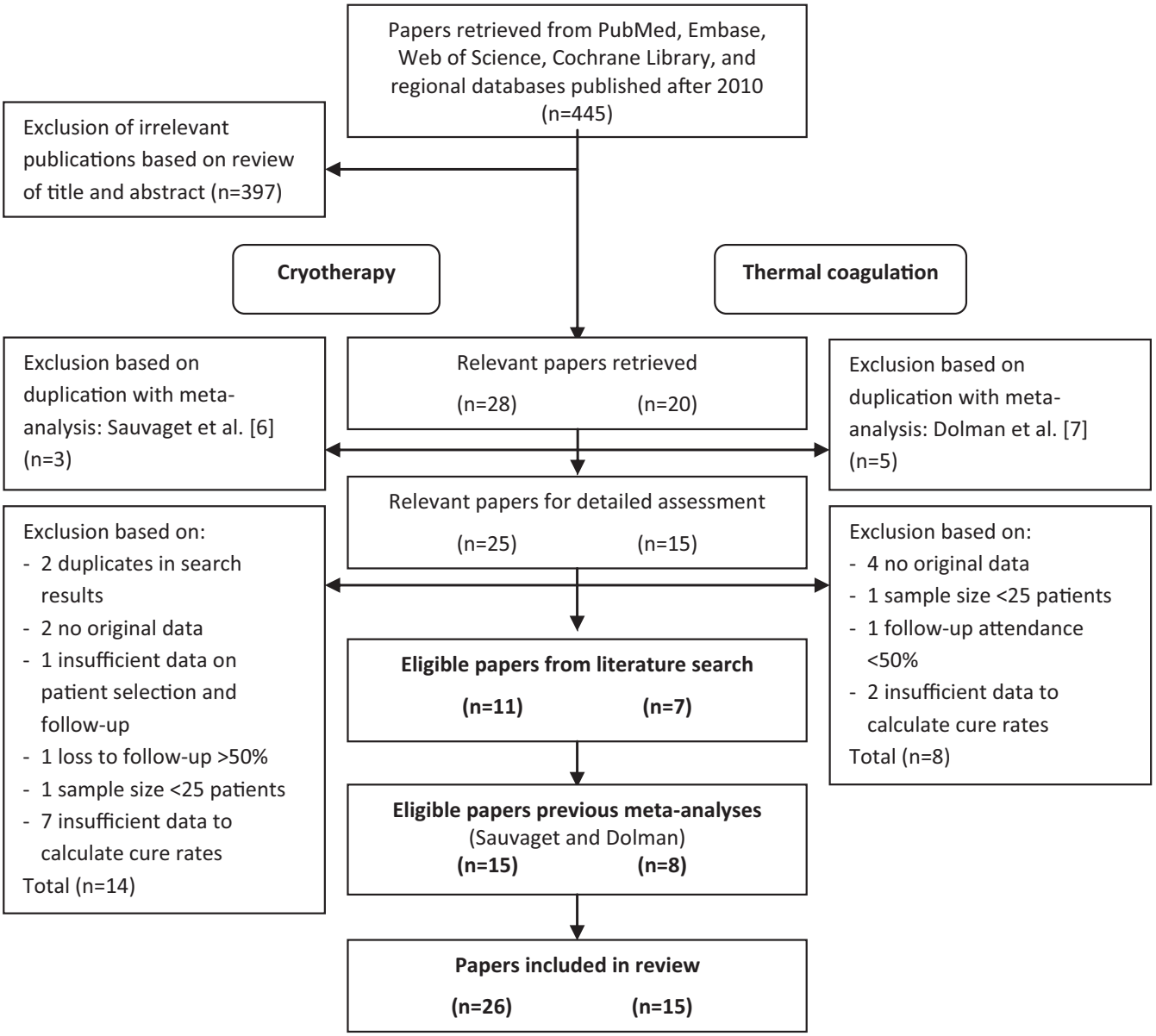

FIGURE 1 Flowchart summarizing literature search and included studies. In total 40 original papers were included, Singh et al (1988)[8] reported data on both cryotherapy and thermal coagulation.

3.6 | HIV status

For both treatment modalities, only two studies published cure proportions for HIV-positive patients specifically. Table S8 presents all studies with cure rates for HIV-positive patients. Data on outcome of HIV-positive patients specifically was too limited to allow statistical testing.

3.7 | Treatment technique and provider

In contrast to cryotherapy studies conducted in the 1970s and 1980s that make up most of the papers in the review by Sauvaget et al.,[6] almost all cryotherapy papers used the internationally recommended double-freeze technique. Three papers did not specify the treatment procedure.

For thermal coagulation, treatment procedures varied with temperatures ranging from 100–120°C and treatment duration from 20–60 seconds. All studies used repeated treatment cycles with a maximum of four cycles per patient. Due to the heterogeneity in treatment procedures and patient populations, there were insufficient data for statistical testing of the effect of treatment protocol on cure rate.

In 12 out of 15 papers on thermal coagulation, treatment was provided by physicians. Cryotherapy was more frequently provided by nurses (n=5) or by nurses and physicians (n=4).

3.8 | Pain, adverse effects, and fertility

Pain during and after treatment was discussed in seven papers (47%) on thermal coagulation. Three papers (38%) reported mild cramps or

TABLE 1 Studies included in this meta-analysis for cryotherapy and thermal coagulation.

Author and reference	Publication year	Country	Study year	Setting	Study design	Single visit approach	Age of participants, y	Case definition	Confirmed by biopsy	HIV-status known	Treatment provider	Duration of follow-up	Number of women treated	Cure definition
Cryotherapy														
Singh[8]	1988	Singapore	1983–1988	Hospital (III)	RCT	No	Mean 35 (20–50)	CIN 1–3	Yes	No	Colposcopist	3 months–4 years (79.4% for >1 year)	68	Negative colposcopy, cytology and biopsy
Omigbodun[21]	1991	Nigeria	1984–1988	Hospital (III)	Clinical report	No	Mean 35.4/38.8 (SD 10.0/10.2)	CIN 1–2	Yes	No	Gynecologist	Median 15 months (3–48)	33	Negative cytology
Olatunbosun[22]	1992	Nigeria	1982–1984	Hospital (III)	Clinical report	No	Mean 28 (18–56)	CIN 1–3	Yes	No	Gynecologist	12 months	70	No evidence of CIN
Doh[23]	1999	Cameroon	1994–1996	Hospital (III)	Clinical report	No	20 to >60 (88.3% 30–49)	CIN 1–3	Yes	No	Gynecologist	12 months or more	100	No persistent CIN
Chirenje[24]	2001	Zimbabwe	1997–1998	Hospital (III)	RCT	No	Mean 32.5 (SD 6.1)	HSIL	Yes	No	Gynecologist	12 months	161	Negative colposcopy, cytology or biopsy
Chirenje[14]	2003	Zimbabwe	1997–1998	Hospital (III)	RCT	No	Mean 31 (SD 5.2)	CIN 2–3	Yes	Yes	Gynecologist	12 months	61	Negative cytology
Sankaranarayanan[a,25]	2007	India	2000–2003	Hospital (I)	Clinical report	Yes	30–59	CIN 1–3	Yes	No	Nurse	12 months	1026	Absence of CIN
Aerssens[26]	2008	Nicaragua	2001–2005	Hospital (I)	Clinical report	No	Mean 33.6	CIN 1	Yes	No	Gynecologist	Mean 622 days (14–1240 days)	55	Negative colposcopy, cytology or biopsy
Chumworathayi[27]	2008	Thailand	2001	Hospital (III)	Clinical report	Yes	Mean 38 (31–46)	VIA+	No	No	Nurse	12 months	648	Negative VIA, colposcopy and biopsy

(Continues)

TABLE 1 (Continued)

Author and reference	Publication year	Country	Study year	Setting	Study design	Single visit approach	Age of participants, y	Case definition	Confirmed by biopsy	HIV-status known	Treatment provider	Duration of follow-up	Number of women treated	Cure definition
Luciani[28]	2008	Peru	2000–2004	Hospital (I)	Clinical report	Yes	25–49 (84% 25–39)	CIN 1–3	Yes	No	Primary care physician	12 months	472	Negative VIA and cytology, if found positive cured if negative biopsy
Nene[29]	2008	India	Not documented	Hospital (I)	RCT	No	30-59	CIN 1–3	Yes	No	Nurse	Mean 30 months (8–36 or more)	574	Absence of CIN
Bhatla[30]	2009	India	2004–2005	Hospital (I)	Clinical report	No	25–59 (82.7% 25–44)	CIN 1–3	Yes	No	Physician	12 months	31	No evidence of disease (no details given)
Poomtavorn[31]	2009	Thailand	2004–2008	Hospital (III)	Clinical report	No	Mean 36.2 (SD 9.4)	CIN 1	Yes	No	Gynecologist	12 months	26	Absence of CIN
Chumworathayi[32]	2010	Thailand	2007–2009	Hospital (III)	RCT	No	Mean 42 (SD 7.86)	LSIL, HPV+ and >30	Yes	Yes	Not documented	6 and 12 months	29	Negative colposcopy, cytology and biopsy
Cremer[33]	2010	Salvador	2006–2007	Hospital (I)	Clinical report	No	Mean 34.1 (SD 9.7)	VIA+	Yes	No	Gynecologist	Up to 3 years	18	Absence of CIN 2
Denny[34]	2010	South Africa	2000-2002	Hospital (I)	Clinical report	Yes	Mean 43.3 (35–65)	HPV+ and VIA+	No	No	Nurse	36 months	4388	Absence of CIN 2
Phongsavan[35]	2011	Laos	2009–2010	Hospital (II)	Clinical report	Yes	Mean 34 (25–45)	VIA+	No	No	Nurse and Gynecologist	12 months	75	Absence of VIA+
Vet[36]	2012	Indonesia	2004–2006	Mobile clinics	Clinical report	Yes	Mean 37.5 (12–70)	VIA+	Yes	No	Nurse and physician	6 months	918	Absence of VIA and normal cytology

(Continues)

TABLE 1 (Continued)

Author and reference	Publication year	Country	Study year	Setting	Study design	Single visit approach	Age of participants, y	Case definition	Confirmed by biopsy	HIV-status known	Treatment provider	Duration of follow-up	Number of women treated	Cure definition
Levinson[37]	2013	Peru	2009	Health clinics	Clinical report	No	Mean 36 and 37 (in 2 regions)	hrHPV+ and VIA+	No	No	Not documented	6 months	57	Negative colposcopy, biopsy and HPV test
Wesley[38]	2013	India	2001–2008	Regional cancer center	Clinical report	No	57.8% <40	CIN 1–3	Yes	No	Nurse and physician	12 months or more	211	Absence of CIN
Chigbu[39]	2014	Nigeria	2011–2012	Not documented	Clinical report	Yes	Mean 36 (SD 2.3)	VIA+	No	No	Gynecologist	6 months	205	Absence of VIA+
Starks[40]	2014	Mexico	2008–2009	HPV-self screening	Clinical report	Not documented	Median 38.8 (30–53)	hrHPV+ and VIA+	Yes	No	Not documented	6 months	291	Absence of CIN
De Vuyst[41]	2014	Kenya	2009	Hospital	Clinical report	No	Median 41 (IQR 35–45)	CIN 2–3	Yes	Yes	Not documented	6 months	101	Absence of CIN 2–3
Chigbu[42]	2017	Nigeria	2011–2014	Health clinics (rural)	Clinical report	Yes	Mean 43.6 (SD 6.3)	VIA+	Yes	No	Nurse and physician	12 months	64	Absence of VIA+ and CIN
Firnhaber[43]	2017	South Africa	2012–2015	Hospital HIV-clinic	RCT	Yes	Mean 37.2 (32.7–43.5)	CIN 1 and HIV+	Yes	Yes	Nurse	12 months	112	Absence of CIN 2–3
Smith[44]	2017	South Africa	2010–2014	Hospital (III)	RCT	No	Mean 37.5 (26–52)	CIN 2–3 and HIV+	Yes	Yes	Not documented	6 and 12 months	80	Absence of CIN 2–3
Tai[45]	2017	Taiwan	2004–2007	National registry	Retrospective cohort study	Not documented	Not documented	LSIL	No	No	Not documented	35574 person years	7352	Absence of CIN 3
Thermal coagulation														
Staland[46]	1978	Sweden	1971–?	Hospital (III)	Clinical report	No	Not documented	CIN 2–3	No	No	Gynecologist	80% >2 years	71	Negative colposcopy and cytology

(Continues)

TABLE 1 (Continued)

Author and reference	Publication year	Country	Study year	Setting	Study design	Single visit approach	Age of participants, y	Case definition	Confirmed by biopsy	HIV-status known	Treatment provider	Duration of follow-up	Number of women treated	Cure definition
Javaheri[47]	1981	USA	1974–1979	Hospital (III)	Clinical report	No	15 to >50 (>80% 20–40)	CIN 1–2	Yes	No	Physician	1–5 years	43	Absence of CIN (defined by cytology)
Singh[8]	1988	Singapore	1983–1988	Hospital (III)	RCT	No	Mean 35.2 (SD 7.2)	CIN 1–3	Yes	No	Colposcopist	3 months–4 years (79.4% for >1 year)	89	Negative colposcopy, cytology and biopsy
Gordon[48]	1991	UK	1975–1989	Hospital (III)	Clinical report	Yes	15 to >50 (75% <35)	CIN 3	Yes	No	Colposcopist	4 months (98%) to 10 years (87%)	1661	Negative cytology
Rogstad[49]	1992	UK	1988–1989	Hospital (III)	Clinical report	No	Not documented	CIN 1–2	Yes	No	Physician	6–12 months	60	Negative cytology
Loobuyck[50]	1993	UK	1978–1990	Hospital (III)	Clinical report	Yes	Not documented	CIN 1–2	Yes	No	Colposcopist	6 months–11 years	1204	Negative cytology
Williams[51]	1993	UK	1988–1989	Hospital (III)	Clinical report	No	Mean 24.5 (range 16–46)	CIN 2–3	Yes	No	Physician	12–18 months	125	Negative colposcopy and cytology
Joshi[9]	2013	India	2012–2013	Screening clinic	Clinical report	Yes	21–57 (mean not given)	CIN 1–3	Yes	Yes	Physician	6–9 months	83	No evidence of disease (not detailed)
Parry-Smith[52]	2015	UK	2001–2011	Hospital (non-university)	Clinical report	No	Median 27 (18–57)	CIN 1–3	Yes	No	Colposcopist	1 year (median 406 days)	614	Negative cytology
Campbell[53]	2016	Malawi	2013–2015	Rural hospital and health centers	Clinical report	Yes	16–86 (mean not given)	VIA+	No	Yes	Non-physician	3–6 months	381	Absence of VIA+
McCarthy[54]	2016	Ireland	2009–2010	Hospital (III)	Clinical report	No	Mean 29.2 (SD 5.5)	CIN 1–3	Yes	No	Physician	3 years	93	Negative cytology

(Continues)

TABLE 1 (Continued)

Author and reference	Publication year	Country	Study year	Setting	Study design	Single visit approach	Age of participants, y	Case definition	Confirmed by biopsy	HIV-status known	Treatment provider	Duration of follow-up	Number of women treated	Cure definition
Naud[55]	2016	Brazil	2012–2013	Hospital (III)	Clinical report	No	Median 31 (27–40)	CIN 2–3	Yes	No	Physician	1 year	52	Negative VIA and cytology or colposcopy or biopsy
Oga[56]	2016	Nigeria	2010–2014	Hospital (different levels)	Clinical report	Yes	Mean 34.9 (SD 7.4)	VIA+ or VILI+	No	Yes	Nurse	6 months (median 531 days)	262	Negative VIA or VILI
Tran[57]	2017	Cameroon	2015	Mobile clinics	Clinical report	Yes	Mean 38.7 (SD 5.3)	HPV+ and VIA+	Yes	No	Not documented	6–12 months (median 8.4 and 14.5 months)	121	Absence of HSIL at cytology or CIN 2 at biopsy
Wyse[58]	2017	Ireland	2014–2015	Hospital (non-university)	Clinical report	No	Mean 31 (SD 6.37)	CIN 1–3	Yes	No	Colposcopist	6 months	200	Negative cytology

Abbreviations: RCT, randomized controlled trial; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HPV, human papillomavirus (hr=high risk); VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol iodine; SD, standard deviation; CIN, cervical intraepithelial neoplasia.

[a]Chirenje et al. (2003)[14] reported proportions of cure specific for HIV-positive patients of the cohort for which the overall proportion of cure was reported in the previous paper by Chirenje et al. (2001).[24]

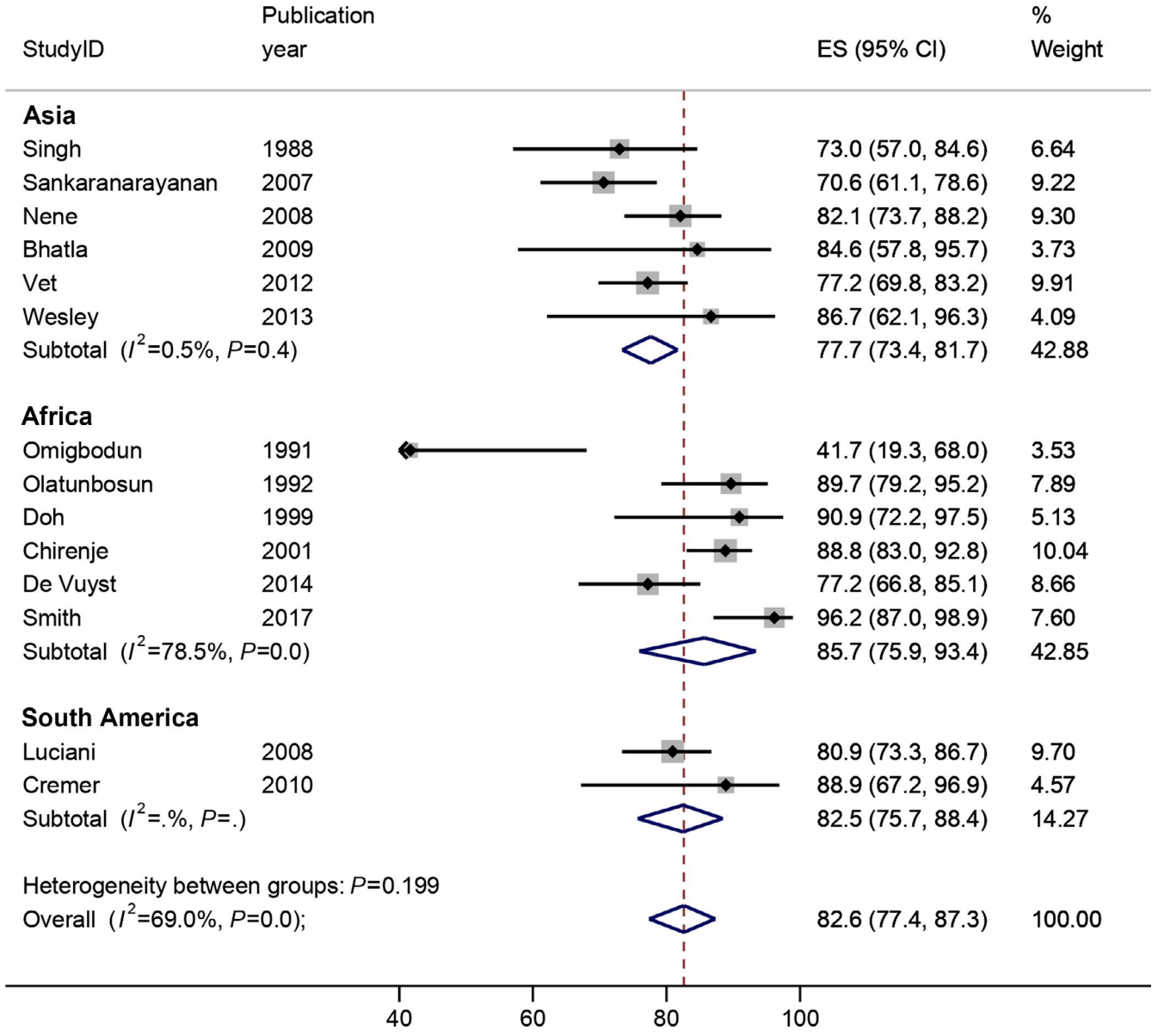

FIGURE 2 Cure proportions for CIN 2–3 lesions treated with cryotherapy grouped by region.

pain in 21%, 25%, and 79% of patients. In contrast, Rogstad et al.[49] stated treatment is painful without further details. Parry-Smith et al.[52] reported routine use of local anesthesia for thermal coagulation. Naud et al.[55] reported a heat sensation in the vagina for 1 in 4 patients during treatment.

Twelve papers (46%) on cryotherapy reported pain, varying from 1% to 30% of patients complaining of mild pain and cramps during treatment to less than 1% experiencing severe pain or cramps. Vet et al.[36] reported routine use of oral analgesics after cryotherapy in Indonesia.

Adverse reactions and complications were reported inconsistently and rarely for both treatment modalities. Table S9 shows the adverse reactions reported in 6 (40%) thermal coagulation and 15 (58%) cryotherapy papers. Fertility outcomes and pregnancy outcomes were also rarely reported. For each treatment modality, three papers mentioned subsequent pregnancies in treated patients, and three of these papers reported normal outcomes.

4 | DISCUSSION

4.1 | Main findings

The present review aimed to compare the effectiveness of thermal coagulation versus cryotherapy with focus on LMICs because the sustainability of cervical cancer screening programs in LMICs is impaired by practical and technical challenges with cryotherapy. According to our findings, both cryotherapy and thermal coagulation are effective treatments for CIN lesions based on cure proportions, ranging from 90.1% to 92.8% for VIA-positive lesions, 91.4% to 93.8% for CIN 1, and 82.6% to 91.6% for CIN 2–3 lesions.

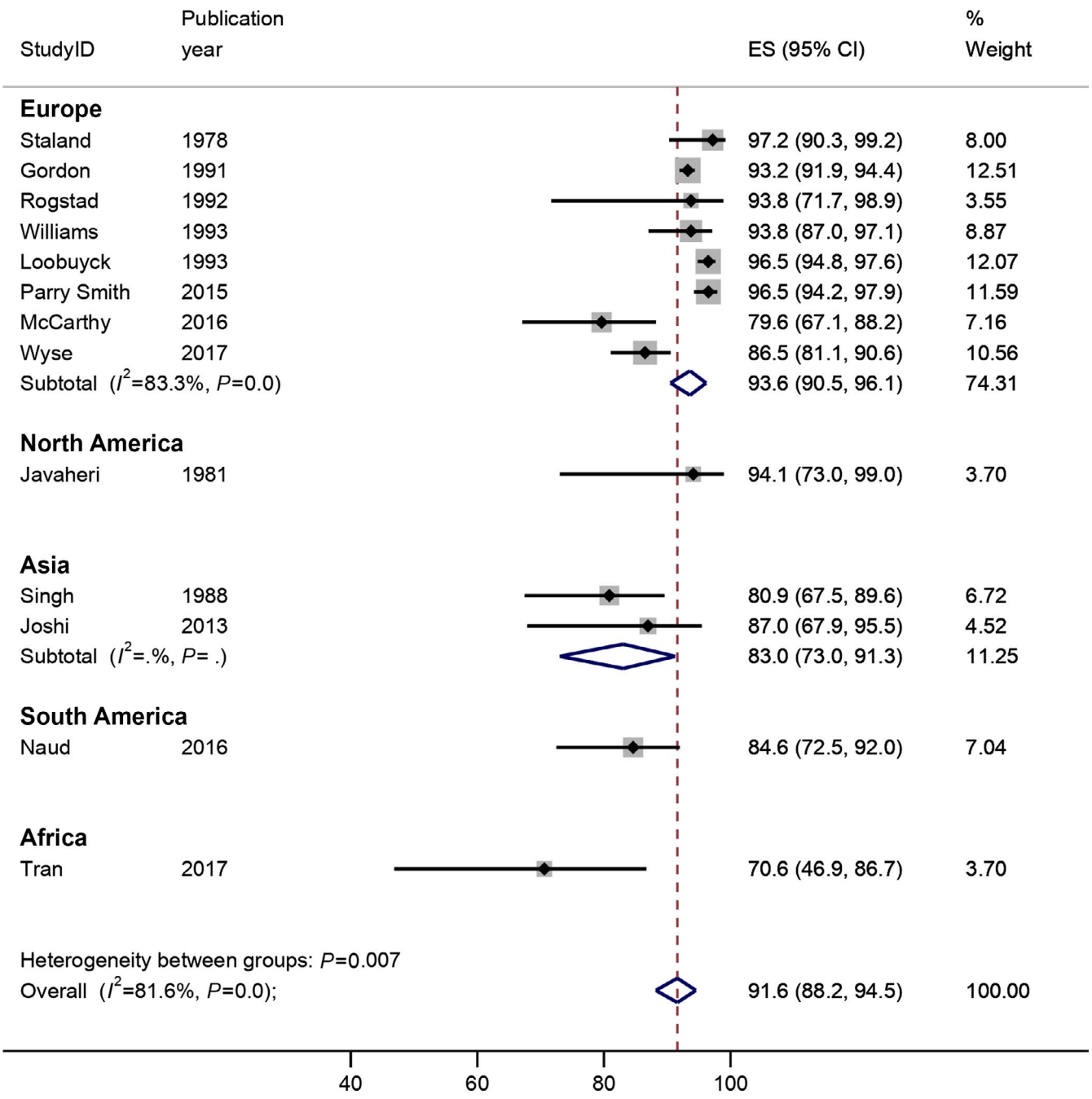

FIGURE 3 Cure proportions for CIN 2–3 lesions treated with thermal coagulation grouped by region.

Our findings suggest a difference between the treatment effectiveness for CIN 2–3 lesions in favor of thermal coagulation. However, when comparing the effectiveness of both treatment modalities in LMICs only, the proportion of cure was similar: 82.6% for cryotherapy and 82.4% for thermal coagulation.

Cure proportions in HIV-positive patients did not suggest a higher risk of treatment failure compared with the overall target population, but data on this topic were limited and previous studies have shown increased risk of treatment failure.[56,59] Patients' experiences of pain, adverse effects, and obstetric outcomes were inconsistently reported. For both treatment modalities, patient acceptability appeared to be good without routine use of local anesthesia, and both treatment modalities were reportedly safe. Treatment modalities should be selected based on local available resources in LMICs to achieve high uptake of direct treatment in a single-visit approach.

4.2 | Interpretation

The cure proportions were comparable to previous reviews of cryotherapy (94.0% for CIN 1, 92.0% for CIN 2, 85.0% for CIN 3 lesions, and 89.9%–91.9% for all CIN grades), although they were

TABLE 2 Summary of the included studies (n=41).

	Cryotherapy	Thermal coagulation
No. of studies	26	15
No. of studies from LMICs (%)	26 (100)	6 (40)
No. of studies with a single visit (%)	9 (35)	6 (40)
No. of studies with data on HIV-positive patients (%)	6 (23)	3 (20)
No. of patients with follow-up data	12 915	4501
CIN 1 (%)	9815 (76.0)	788 (17.5)
CIN 2–3 (%)	955 (7.4)	3302 (73.4)
VIA-positive (%)	2145 (16.6)	411 (9.1)
Follow-up attendance (median %, range)	86.7 (55.3–100)	96.2 (52.3–100)
CIN 1	89.0 (55.3–100)	100.0 (56.4–100)
CIN 2–3	86.7 (65.4–100)	98.0 (52.3–100)
VIA-positive	76.6 (68.1–92.1)	64.5 (61.4–67.6)
Follow-up duration, mo. (%)		
6	5 (19.2)	4 (26.7)
12	20 (76.9)	11 (73.3)
Missing	1 (3.8)	–

Abbreviation: LMICs, low- and middle-income countries.

slightly lower compared with a previous meta-analysis of thermal coagulation (96.0% for CIN 1 and 95.0% for CIN 2–3 lesions).[6,7,60] The lower proportions of cure found for thermal coagulation can be explained by an increased number of papers from LMICs in the present review.[7] A retrospective analysis of thermal coagulation in Bangladesh, Brazil, and India by Nessa et al.[61] found cure proportions ranging from 83% to 88% for CIN 1–3 lesions. This paper was not included in the present review owing to more than 50% loss to follow-up.

Furthermore, we employed a different strategy to assess study quality and used stricter inclusion criteria, excluding studies with follow-up duration of less than 6 months and sample size smaller than 25 patients. It is unlikely though that the stricter inclusion criteria explained the difference in pooled cure proportions. The studies excluded from the previous meta-analysis, Hussein et al.[17] and de Cristofaro et al.,[18] represented 53 patients with CIN 1 and 128 patients with CIN 3 lesions.

In contrast to previous reviews, we included outcomes of VIA-based programs. The presented pooled proportion of cure for VIA-based programs might be an overestimation of the actual proportion of cure at follow-up due to over-diagnosis of precancerous lesions with VIA-assessment and thus overtreatment of patients without cytological- or histological-proven CIN lesions.[33,62] Most single-visit programs in LMICs are based on VIA screening. The follow-up attendance for VIA-based programs included in this review was 65%–77% and is likely even lower in programs not involved in research. The cure proportions reported underline the importance of follow-up attendance to detect persistent or recurrent lesions as early as possible.

Across the studies, reported cure proportions in Africa, Asia, and South America were low compared with Europe and North America. Most studies in Europe and North America are conducted in tertiary hospitals, with physicians and specialists providing diagnosis and treatment in well-controlled screening programs, where bigger lesions are frequently treated with excisional techniques such as LEEP. Another explanation is the higher prevalence of HIV infection in parts of Africa, Asia, and South America. Most studies did not detail the HIV-positivity rate of their patients, nor did they provide details on their proportion of cure. This is a shortcoming in the currently available data and an important field of research because HIV-positive patients are at increased risk of cervical cancer and treatment failure.[2,41,59,60] Besides HIV infection, HPV infection is more prevalent in LMICs.[63] In Sub-Saharan Africa and South America, the prevalence of HPV in women with normal cytological findings was 24% and 16.1%, respectively, compared with 14.2% in Europe.[63] The higher prevalence of HPV in the general population, in Sub-Saharan Africa especially, might lead to a lower HPV clearance and higher reinfection rate after treatment.[32,63,64]

The present review included papers with cure proportion as the primary outcome and is not representative of all literature published on pain, adverse effects, fertility outcomes, and obstetric outcomes. A systematic review of the adverse effects and benefits of cryotherapy found that complications such as major bleeding and organ damage are extremely rare (RR <0.05) but reported low-quality evidence.[65] There are currently no reviews on the adverse effects of thermal coagulation. Viviano et al.[66] reported, in a study in Cameroon, a mean visual analogue score of 3.0 ± 1.6 during treatment.

A Cochrane review[67] found an increased risk of premature delivery in women with CIN lesions, with a lower relative risk for ablative techniques (RR 1.35; 95% CI, 1.20–1.52) compared with excisional techniques (RR 1.87; 95% CI, 1.64–2.12). However, evidence is of low quality and mainly based on retrospective studies. Ongoing documentation of adverse effects and pregnancy outcomes is important but difficult to achieve in practice.

4.3 | Limitations

We attempted to identify all papers published on cryotherapy and thermal coagulation for treatment of CIN lesions, with focus on LMICs. However, there are limitations to the data and findings presented. Papers published before 2010 on cryotherapy in LMICs might have been missed because Sauvaget et al.[6] used less inclusive keywords in their literature search ("cervical intraepithelial neoplasia," "CIN," and "cryotherapy") and regional databases were not included. We believe this difference will be minimal, based on our literature search with 129 unique references identified in regional databases, of which only one abstract was found to be relevant and the full article did not meet the inclusion criteria. Despite recent publications on thermal coagulation from Asia, Africa, and South America, most studies have been conducted in Europe and North America. Data on cryotherapy from LMICs exceed that of thermal coagulation, both in number of studies and sample size.

The studies show great heterogeneity in terms of sample size, treatment protocol, and follow-up duration. Additionally, not all papers detailed the achieved follow-up duration, loss to follow-up, or included only patients attending follow-up visits in their data. This might lead to misinterpretation of cure proportions. Sensitivity analysis found higher cure proportions for cryotherapy papers with greater than 75% follow-up attendance, demonstrating the impact of follow-up on reported cure proportions. We found few studies with nonphysician clinicians as treatment providers. It is important that more data are collected from programs with nonphysician clinicians because this will be the reality for most women screened in low-resource settings.

4.4 | Future recommendations

In future, more HPV-based screening programs will be implemented in LMICs, with higher treatment rates expected due to higher sensitivity of HPV testing compared with VIA/VILI and cytology.[62] This approach will yield greater health benefits than VIA-based programs in low-resource settings where cervical cancer incidence is high.[68] A widely available, acceptable, and effective treatment method is necessary. Thermal coagulation is a promising alternative to cryotherapy with comparable proportions of cure, which will enhance the sustainability of screening programs in LMICs and make a significant contribution to the fight against the burden of cervical cancer worldwide. We recommend that more studies including randomized controlled trials are conducted to compare thermal coagulation and cryotherapy in LMICs to assess efficacy, safety, and provider and patient experience. For practical implications, future studies should focus on the risk of treatment failure in HIV-positive patients for both treatment modalities, the effect of different treatment protocols for thermal coagulation on proportions of cure, and report pain and adverse effects consistently.

AUTHOR CONTRIBUTIONS

MF reviewed the study design, carried out the final literature search and review, conducted data extraction and analysis, and drafted the manuscript. RO initiated the study, carried out the literature search during the orientation phase of the study, carried out data extraction and analysis, and participated in writing the final manuscript. AR initiated the study, carried out the literature search during the orientation phase of the study, assisted in data extraction, and participated in writing the final manuscript. OD carried out data analysis and participated in writing the final manuscript. JB supervised the study design, data analysis and interpretation, and participated in writing the final manuscript. AW supported data interpretation and participated in writing the final manuscript. All authors reviewed and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjamataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
2. World Health Organization. WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. Published 2013. http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/. Accessed February 10, 2018.
3. Cervical Cancer Action. Global progress in visual inspection (VIA) for cervical cancer screening. 2017. http://www.cervicalcanceraction.org/comments/comments.php. Accessed February 10, 2018.
4. Castle PE, Murokora D, Perez C, Alvarez M, Chong Quek S, Campbell C. Treatment of cervical intraepithelial lesions. *Int J Gynecol Obstet*. 2017;138(Suppl.1):20–25.
5. Maza M, Schocken CM, Bergman KL, Randall TC, Cremer ML. Cervical precancer treatment in low- and middle-income countries: a technology overview. *J Glob Oncol*. 2016;3:400–408.
6. Sauvaget C, Muwonge R, Sankaranarayanan R. Meta-analysis of the effectiveness of cryotherapy in the treatment of cervical intraepithelial neoplasia. *Int J Gynecol Obstet*. 2013;120:218–223.
7. Dolman L, Sauvaget C, Muwonge R, Sankaranarayanan R. Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: A systematic review. *BJOG*. 2014;121:929–942.
8. Singh P, Loke KL, Hii JHC, et al. Cold coagulation versus cryotherapy for treatment of cervical intraepithelial neoplasia: Results of a prospective randomized trial. *Colposcopy Gynecol Laser Surg*. 1988;4:211–221.
9. Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. *AIDS*. 2013;27:607–615.
10. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4949.
11. Adewole IF, Babarinsa IA, Odeniyi GD. Cryotherapy in the management of cervical intraepithelial neoplasia in developing countries. *Int J Gynecol Obstet*. 1998;60:69–70.

12. Leiman G, Andronikou AD. Cryotherapy of the uterine cervix: An inadequate treatment modality in a newly screened population. *S Afr Med J*. 1980;57:39–43.
13. Lewis K, Sellors J, Dawa A, Tsu V, Kidula N. Report on a cryotherapy service for women with cervical intraepithelial neoplasia in a district hospital in western Kenya. *Afr Health Sci*. 2011;11:370–376.
14. Chirenje ZM, Rusakaniko S, Akino V, Munjoma M, Mlingo M. Effect of HIV disease in treatment outcome of cervical squamous intraepithelial lesions among Zimbabwean women. *J Low Genit Tract Dis*. 2003;7:16–21.
15. Blumenthal PD, Lauterbach M, Sellors JW, Sankaranarayanan R. Training for cervical cancer prevention programs in low-resource settings: Focus on visual inspection with acetic acid and cryotherapy. *Int J Gynecol Obstet*. 2005;89(Suppl.2):S30–S37.
16. Goodman JD, Sumner D. Patient acceptability of laser and cold coagulation therapy for pre-malignant disease of the uterine cervix. *BJOG*. 1991;98:1168–1171.
17. Hussein IY, Galloway RK. Use of cold coagulator in the treatment of cervical intraepithelial neoplasia. *J Obstet Gynecol*. 1985;6:62–64.
18. de Cristofaro D, Trioni G, Pezzoli C. Treatment of CIN with cold coagulation. *J Exp Clin Cancer Res*. 1990;9:133.
19. Cassidy LJ, Mathers A, Kennedy JH. Cold coagulation revisited. *Colposcopy Gynecol Laser Surg*. 1987;3:232.
20. Grubisic G, Vukosavic-Cimic B, Kraljevic Z, Pirkic A, Grbavac I, Bolanca I. Cytologic follow-up in patients with CIN treated by LLETZ, cold knife conization and Semm's cold coagulation. *Coll Antropol*. 2010;34:13–17.
21. Omigbodun AO. Management of cervical intraepithelial neoplasia where colposcopy is not available. *Cent Afr J Med*. 1991;37:7–11.
22. Olatunbosun OA, Okonofua FE, Ayangade SO. Outcome of cryosurgery for cervical intraepithelial neoplasia in a developing country. *Int J Gynecol Obstet*. 1992;38:305–310.
23. Doh AS, Kouam L. The management of pre-invasive cervical lesions using cryotherapy in Yaounde, Cameroon. *J Obstet Gynecol*. 1999;19:640–642.
24. Chirenje ZM, Rusakaniko S, Akino V, Mlingo M. A randomised clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia. *J Obstet Gynecol*. 2001;21:617–621.
25. Sankaranarayanan R, Rajkumar R, Esmy PO, et al. Effectiveness, safety and acceptability of "see and treat" with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer*. 2007;96:738–743.
26. Aerssens A, Claeys P, Garcia A, et al. Natural history and clearance of HPV after treatment of precancerous cervical lesions. *Histopathology*. 2008;52:381–386.
27. Chumworathayi B, Srisupundit S, Lumbiganon P, Limpaphayom KK. One-year follow-up of single-visit approach to cervical cancer prevention based on visual inspection with acetic acid wash and immediate cryotherapy in rural Thailand. *Int J Gynecol Cancer*. 2008;18:736–742.
28. Luciani S, Gonzales M, Munoz S, Jeronimo J, Robles S. Effectiveness of cryotherapy treatment for cervical intraepithelial neoplasia. *Int J Gynecol Obstet*. 2008;101:172–177.
29. Nene BM, Hiremath PS, Kane S, Fayette JM, Shastri SS, Sankaranarayanan R. Effectiveness, safety, and acceptability of cryotherapy by midwives for cervical intraepithelial neoplasia in Maharashtra, India. *Int J Gynecol Obstet*. 2008;103:232–236.
30. Bhatla N, Gulati A, Mathur SR, et al. Evaluation of cervical screening in rural North India. *Int J Gynecol Obstet*. 2009;105:145–149.
31. Poomtavorn Y, Suwannarurk K, Thaweekul Y, Maireang K. Cervical cytologic abnormalities of cervical intraepithelial neoplasia 1 treated with cryotherapy and expectant management during the first year follow-up period. *Asian Pac J Cancer Prev*. 2009;10:665–668.
32. Chumworathayi B, Thinkhamrop J, Blumenthal PD, Thinkhamrop B, Pientong C, Ekalaksananan T. Cryotherapy for HPV clearance in women with biopsy-confirmed cervical low-grade squamous intraepithelial lesions. *Int J Gynecol Obstet*. 2010;108:119–122.
33. Cremer M, Bullard K, Maza M, et al. Cytology versus visual inspection with acetic acid among women treated previously with cryotherapy in a low-resource setting. *Int J Gynecol Obstet*. 2010;111:249–252.
34. Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC Jr. Human papillomavirus-based cervical cancer prevention: Long-term results of a randomized screening trial. *J Natl Cancer Inst*. 2010;102:1557–1567.
35. Phongsavan K, Phengsavanh A, Wahlstrom R, Marions L. Safety, feasibility, and acceptability of visual inspection with acetic acid and immediate treatment with cryotherapy in rural Laos. *Int J Gynecol Obstet*. 2011;114:268–272.
36. Vet JNI, Kooijman JL, Henderson FC, et al. Single-visit approach of cervical cancer screening: See and Treat in Indonesia. *Br J Cancer*. 2012;107:772–777.
37. Levinson KL, Abuelo C, Salmeron J, et al. The Peru Cervical Cancer Prevention Study (PERCAPS): The technology to make screening accessible. *Gynecol Oncol*. 2013;129:318–323.
38. Wesley RS, Muwonge R, Sauvaget C, Thara S, Sankaranarayanan R. Effectiveness of cryotherapy for histologically confirmed cervical intraepithelial neoplasia grades 1 and 2 in an Indian setting. *Int J Gynecol Obstet*. 2013;123:16–20.
39. Chigbu CO, Onyebuchi AK. Use of a portable diathermy machine for LEEP without colposcopy during see-and-treat management of VIA-positive cervical lesions in resource-poor settings. *Int J Gynecol Obstet*. 2014;125:99–102.
40. Starks D, Arriba LN, Enerson CL, et al. Mexican cervical cancer screening study II: 6-month and 2-year follow-up of HR-HPV women treated with cryotherapy in a low-resource setting. *J Lower Gen Tract Dis*. 2014;18:333–337.
41. De Vuyst H, Mugo NR, Franceschi S. Residual disease and HPV persistence after cryotherapy for cervical intraepithelial neoplasia grade 2/3 for HIV-positive women in Kenya. *PLoS ONE*. 2014;9:e111037.
42. Chigbu CO, Onyebuchi AK, Nnankenyi EF, Egbuji CC. Impact of visual inspection with acetic acid plus cryotherapy "see and treat" approach on the reduction of population burden of cervical preinvasive lesions in Southeast Nigeria. *Niger J Clin Pract*. 2017;20:239–243.
43. Firnhaber C, Swarts A, Goeieman B, et al. Cryotherapy reduces progression of cervical intraepithelial neoplasia grade 1 in South African HIV-infected women: A randomized, controlled trial. *J Acquire Immune Defic Syndr*. 2017;76:532–538.
44. Smith JS, Sanusi B, Swarts A, et al. A randomized clinical trial comparing cervical dysplasia treatment with cryotherapy vs loop electrosurgical excision procedure in HIV-seropositive women from Johannesburg, South Africa. *Am J Obstet Gynecol*. 2017;217:183.e1–183.e11.
45. Tai YJ, Chen YY, Hsu HC, et al. Clinical management and risk reduction in women with low-grade squamous intraepithelial lesion cytology: A population-based cohort study. *PLoS ONE*. 2017;12:e0188203.
46. Staland B. Treatment of premalignant lesions of the uterine cervix by means of moderate heat thermosurgery using the Semm coagulator. *Ann Chir Gynecol*. 1978;67:112–116.
47. Javaheri G, Balin M, Meltzer RM. Role of cryosurgery in the treatment of intraepithelial neoplasia of the uterine cervix. *Obstet Gynecol*. 1981;58:83–87.
48. Gordon HK, Duncan ID. Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100 degrees C using the Semm cold coagulator: 14 years' experience. *BJOG*. 1991;98:14–20.
49. Rogstad KE, Dixon CA, Ahmed IH. The management of subclinical wart virus infection of the cervix in a genitourinary clinic. *Genitourin Med*. 1992;68:307–308.
50. Loobuyck HA, Duncan ID. Destruction of CIN 1 and 2 with the Semm cold coagulator: 13 years' experience with a see-and-treat policy. *BJOG*. 1993;100:465–468.

51. Williams OE, Bodha M, Alawattegama AB. Outcome of cold coagulation for the treatment of cervical intraepithelial neoplasia in a department of genitourinary medicine. *Genitourin Med*. 1993;69:63–65.
52. Parry-Smith W, Underwood M, De Bellis-Ayres S, Bangs L, Redman CWE, Panikkar J. Success rate of cold coagulation for the treatment of cervical intraepithelial neoplasia: A retrospective analysis of a series of cases. *J Low Genit Tract Dis*. 2015;19:17–21.
53. Campbell C, Kafwafwa S, Brown H, et al. Use of thermo-coagulation as an alternative treatment modality in a 'screen-and-treat' programme of cervical screening in rural Malawi. *Int J Cancer*. 2016;139:908–915.
54. McCarthy CM, Ramphul M, Madden M, Hickey K. The use and success of cold coagulation for the treatment of high grade squamous cervical intra-epithelial neoplasia: A retrospective review. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:225–228.
55. Naud PS, Muwonge R, Passos EP, Magno V, Matos J, Sankaranarayanan R. Efficacy, safety and acceptability of thermocoagulation for treatment of cervical intraepithelial neoplasia in a hospital setting in Brazil. *Int J Gynecol Obstet*. 2016;133:351–354.
56. Oga EA, Brown JP, Brown C, et al. Recurrence of cervical intraepithelial lesions after thermo-coagulation in HIV-positive and HIV-negative Nigerian women. *BMC Womens Health*. 2016;16:25–33.
57. Tran PL, Kenfack B, Foguem ET, et al. Efficacy of thermoablation in treating cervical precancerous lesions in a low-resource setting. *Int J Womens Health*. 2017;9:879–886.
58. Wyse A, Seah WA, O'Neill J, Byrne P. The use of cold coagulation for the treatment of cervical intraepithelial neoplasia. *Ir Med J*. 2017;110:565.
59. Reimers LL, Sotardi S, Daniel D, et al. Outcomes after an excisional procedure for cervical intraepithelial neoplasia in HIV-infected women. *Gynecol Oncol*. 2010;119:92–97.
60. Jacob M, Broekhuizen FF, Castro W, Sellors J. Experience using cryotherapy for treatment of cervical intraepithelial neoplasia. *Obstet Gynecol*. 2005;89(Suppl.2):S13–S20.
61. Nessa A, Naud P, Esmy PO, et al. Efficacy, safety and acceptability of thermal coagulation to treat cervical intraepithelial neoplasia: Pooled data from Bangladesh, Brazil and India. *J Clin Gynecol Obstet*. 2017;6:58–64.
62. Mustafa RA, Santesso N, Khatib R, et al. Systematic reviews and meta-analyses of the accuracy of HPV-tests, visual inspection with acetic acid, cytology and colposcopy. *Int J Gynecol Obstet*. 2016;132:259–265.
63. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: Meta-analysis of 1 million women with normal cytological findings. *J Inf Dis*. 2010;202:1789–1799.
64. Safaeian M, Kiddugavu M, Gravitt PE, et al. Determinants of incidence and clearance of high-risk HPV infections in rural Rakai, Uganda. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1300–1307.
65. Santesso N, Mustafa RA, Wiercioch W, et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP and cold knife conization to treat cervical intraepithelial neoplasia. *Int J Gynecol Obstet*. 2016;132:266–271.
66. Viviano M, Kenfack B, Catarino R, et al. Feasibility of thermal coagulation in a see-and-treat approach for the treatment of cervical pre-cancerous lesions in Sub-Saharan Africa. *BMC Womens Health*. 2017;17:2–10.
67. Kyrgiou M, Athanasiou A, Kalliala IEJ, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. *Cochrane Database Syst Rev*. 2017;11:CD012847.
68. Campos NG, Castle PE, Wright TC Jr, Kim JJ. Cervical cancer screening in low-resource settings: A cost-effectiveness framework for valuing tradeoffs between test performance and program coverage. *Int J Cancer*. 2015;137:2208–2219.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information section at the end of the article.

Data S1. Keywords used in the PubMed literature search. In other databases the same keywords were used, commands were adjusted to the specific database.

Table S1. Overview of studies included in previous meta-analyses but excluded from the present study.

Table S2. Cure proportions for CIN 1 lesions treated with cryotherapy grouped by region.

Table S3. Cure proportions for VIA-positive lesions treated with cryotherapy grouped by region.

Table S4. Cure proportions for CIN 1 lesions treated with thermal coagulation grouped by region.

Table S5. Cure proportions for VIA-positive lesions treated with thermal coagulation grouped by region.

Table S6. Cure proportions for CIN 2–3 lesions treated with thermal coagulation in low- and middle-income countries.

Table S7. Sensitivity analysis of cure proportions for studies with follow-up attendance of 50%–75% and greater than 75%.

Table S8. Cure proportions stratified per lesion and treatment modality for HIV-positive patients.

Table S9. Reported adverse effects and complications, specified by number of studies reporting and percentage of patients affected.