REVIEW ARTICLE

Efficacy of Intralesional Candida Injection in the Treatment of Cutaneous Warts: A Systematic Review and Meta-Analysis

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Recent studies that examined the treatment efficacy of *Candida* antigen injection for both non-genital and genital warts yield inconsistent results. To address this, a systematic review and meta-analysis was conducted, comparing the treatment response between *Candida* antigen injection therapy and other intralesional immunotherapies across all types of warts. PubMed, Cochrane Library, and Embase were searched for relevant randomized controlled trials (RCTs) from inception to 16 September 2023, and 24 eligible RCTs were identified. A protocol was developed using the PRISM A-P checklist. In terms of complete clearance, intralesional *Candida* injection therapy demonstrated a significant improvement compared with saline (risk ratio [RR] 5.39; 95% confidence interval [CI] 3.49–8.33; I^2=0%). However, no statistically significant differences were observed when compared with other therapies such as mumps–measles–rubella vaccines, purified protein derivative, vitamin D3, bivalent human papillomavirus vaccine, and zinc sulphate. Adverse effects associated with intralesional *Candida* therapy were generally reported as mild and manageable. In conclusion, intralesional *Candida* injection therapy for cutaneous warts may exhibit a superior complete and distant response rate. Nevertheless, owing to a limited sample size and other limitations, future research should aim for larger studies to provide more conclusive evidence.

Key words: warts; verruca; immunotherapy; candida; meta-analysis.

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SIGNIFICANCE

Recent studies on Candida antigen injections for treating warts have shown mixed results. This review compared Candida injections with other treatments by analysing 24 studies. Candida injections were better than saline injections for clearing warts but similar to treatments like MMR vaccines and vitamin D3 injections. Side effects were generally mild and manageable. Candida injections might be as effective as other available treatments. Overall, Candida injections might be a good option for treating warts.

Warts are common benign epidermal tumours secondary to human papillomavirus (HPV) infection and may occur on different areas of the body. The primary types of warts include common, flat, plantar, filiform, periungual, mosaic, and genital warts (1).

Currently, various treatment options are available (2). Traditional wart treatments, such as cryotherapy, electrodesiccation, and salicylic acid, are commonly employed; however, the warts have a high recurrence rate. Conversely, current alternative medical wart treatments include injectable immunotherapy, vitamin D3, antiviral medication (cidofovir), topical immunotherapy, chemotherapeutics (bleomycin, 5-fluorouracil), and device-based treatments such as photodynamic therapy and pulsed dye laser. These alternative treatments are more effective and are better tolerated than traditional treatments. Nonetheless, treatment with a 100% cure rate is currently non-existent. Thus, ongoing research is investigating emerging treatments such as nanopulse stimulation technology, ionic contra-viral therapy, and cold atmospheric pressure plasma. The objective is to further increase cure rates while minimizing side effects.

Intralesional immunotherapy is highly effective for treating recalcitrant or multiple warts (3). Delivering antigens directly into the lesion or throughout the body triggers an immune response that promotes clearance of injected warts and aids clearance of distant warts. The most extensively researched agents include *Candida* antigen, measles, mumps, and rubella (MMR) vaccine, purified protein derivative (PPD), and HPV vaccine. Among these, the most well-known intralesional immunotherapy is possibly *Candida* antigen injection, as it requires only one injection site to clear warts in distant areas, exhibiting the lowest rate of recurrence and new wart development (4). A comparative study by Fawzy et al. (5) underscored the efficacy and safety of *Candida* antigen, MMR, and PPD for intralesional immunotherapy of flat warts. The findings indicated a higher rate of complete clearance with *Candida* antigen. Conversely, a network meta-analysis by Salman et al. (6) concluded that PPD and MMR were the most effective treatments for both complete primary and distant recovery of warts. Notably, only 2 out of the

17 studies in the analysis by Salman et al. (6) focused on *Candida* antigen, which suggests that there may not be sufficient robust evidence to draw definitive conclusions concerning its efficacy. Moreover, the studies included in the analysis by Salman et al. (6) encompassed diverse wart types without directly comparing treatment outcomes for each type. This variability may have contributed to inconsistent results. A recent meta-analysis by Ju et al. (7) focused specifically on the efficacy and safety of intralesional immunotherapy for nongenital warts, revealing a lack of systematic investigation into the treatment response of *Candida* antigen injection for both nongenital and genital warts.

Thus, we conducted a systematic review and meta-analysis of all relevant randomized controlled trials (RCTs) to compare the treatment response, recurrence rate, and safety between *Candida* antigen injection therapy and other intralesional immunotherapies across all types of warts.

MATERIALS AND METHODS

We conducted a systematic review and meta-analyses following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines (Table SI) (8). The protocol of this review was registered on PROSPERO (CRD42023484966).

Data sources and search strategy

A systematic electronic search of PubMed, the Cochrane Library, and Embase was conducted from inception to 16 September 2023. We used the following key terms to search the literature (Fig. S1): ([intralesional] AND [Candida]) AND (warts OR verruca OR human papilloma virus). English restrictions were employed. Animal studies were excluded. We also searched for additional studies from the reference lists of primary articles and relevant reviews to find relevant publications not retrieved through the electronic search.

Inclusion and exclusion criteria of the articles

The inclusion criteria were as follows: (1) RCTs; (2) participants in all age groups who have been diagnosed with cutaneous warts who were allowed to receive previous treatment; (3) studies involving the comparison of at least 2 groups of intralesional injection agents, with 1 group requiring the exclusive administration of intralesional *Candida* injection therapy; (4) data were sufficient for conducting an analysis.

The exclusion criteria were as follows: (1) case reports, reviews, retrospective medical analysis, single-arm study, comments, letters, or conference abstracts; (2) duplicated articles; (3) outcomes not relevant; and (4) RCTs that were underway (unpublished articles).

Two investigators (C-H Chang, Z-Y Sung) independently reviewed the titles and abstracts yielded by this comprehensive search and subsequently selected articles according to the predetermined inclusion and exclusion criteria (9). A third reviewer (Y-C Huang) would serve as an arbitrator to address inconsistent viewpoints or disagreements.

Outcomes

The primary outcome of this study was the treatment response rate of intralesional immunotherapy in patients with cutaneous warts, specifically evaluating complete and partial responses. Complete responses were defined as the complete clearance (100%) of cutaneous wart lesions, whereas partial responses were defined as the clearance of 50–99% of wart lesions. The secondary outcomes included clinical response in distant warts and adverse effects.

Data extraction

Data extracted included enrolled patient numbers from each included study, age, number of lesions, type and duration of warts, type of intralesional immunotherapeutic agents, interval, and maximum number of treatment sessions. Wart clearance rate, and adverse effects of treatment were also recorded (Tables SII–SIV). If warranted, we contacted the corresponding authors of the obtained studies to request additional information.

Quality assessment and risk of bias

The quality assessment and risk of bias for this study were conducted following the guidelines outlined in the Cochrane Reviewers' Handbook (3). The Cochrane Risk of Bias Tool 2.0 (RoB 2.0) was used to assess bias risk across 5 specific domains: (*i*) allocation bias, (*ii*) performance bias, (*iii*) attrition bias, (*iv*) detection bias, and (*v*) reporting bias. Each domain was evaluated for low, high, or unclear risk of bias. The overall bias was determined through the highest bias rating. Any discrepancies between the 2 investigators were discussed with a third reviewer.

Statistical analysis

Studies that reported the use of the same type of intralesional injection agents were pooled for meta-analysis. Consequently, the meta-analysis was performed in 6 groups: *Candida* vs placebo (saline group), MMR, PPD, vitamin D3, bivalent HPV vaccine, and zinc sulphate.

Efficacy analysis outcomes were calculated as risk ratios (RR) with 95% confidence intervals (CIs). Heterogeneity was evaluated using p- and I^2 values and subset analyses (10). Under more cautious consideration, we uniformly employed the inverse variance random-effects model for dichotomous outcomes.

Possible publication bias was assessed in the case of ≥ 10 studies using funnel plots. We also used Egger's regression test and the trim and fill test to determine whether publication bias had influenced the results of the meta-analyses (11, 12). All analyses were conducted using RevMan version 5.4 and Comprehensive Meta-Analysis Version 3 (Biostat, Inc, Englewood, NJ, US).

Evaluation of quality of evidence

The assessment of evidence quality for each outcome was performed using GRADEpro GDT (Guideline Development Tool; https://www.gradepro.org/). Consensus was achieved by 2 authors following the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system. In this system, evidence from RCTs is initially rated "high" quality, with the possibility of downgrading according to 5 domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The levels of evidence are categorized on a 4-level scale: very low, low, moderate, or high.

RESULTS

Search results and trial characteristics

Based on the search terms used, 269 eligible articles were retrieved. After removing 76 duplicates, we proceeded to

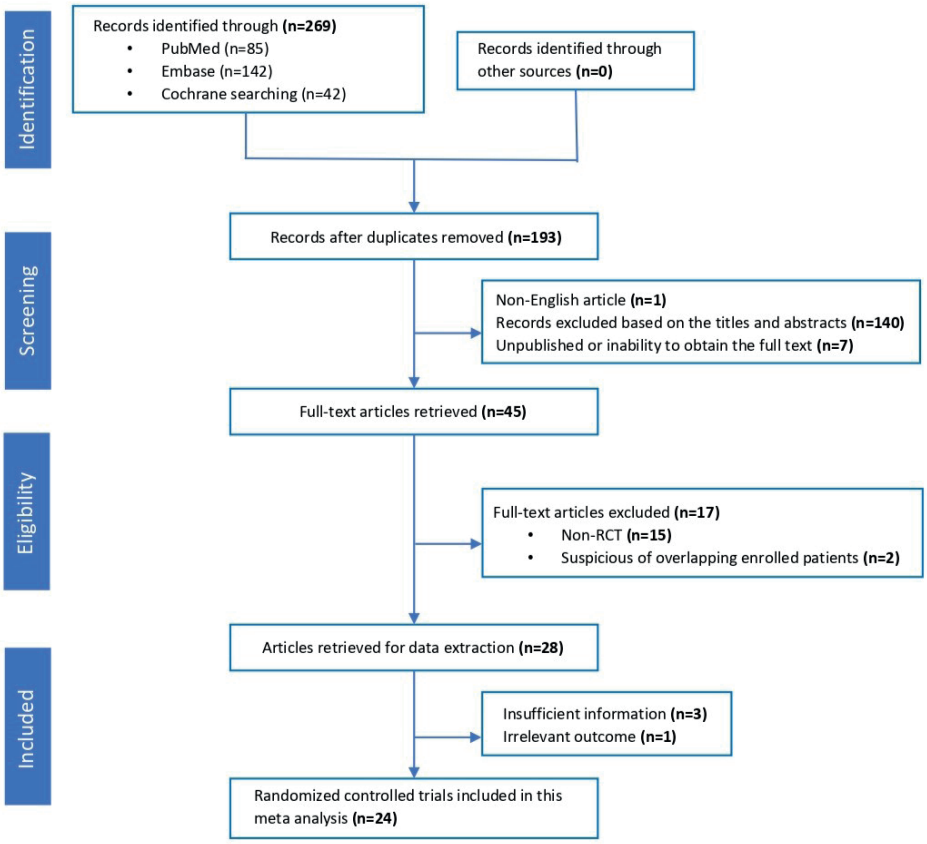

Fig. 1. Flow diagram for selection of eligible studies included in the systematic review and meta-analysis.

select and review the titles and abstracts of the remaining articles. After the removal of 1 non-English trial, 7 unpublished/non-full-text research articles and 140 unrelated articles, 45 articles underwent further review. Finally, after excluding 21 articles that did not satisfy the inclusion criteria, 24 articles were included in the meta-analysis (5, 13–35). The screening process for the literature search is shown in **Fig. 1**.

In our final quantitative analysis, a total of 24 RCTs with 1,982 participants were included. Among these, 11 articles compared saline, 6 with MMR, 7 with PPD, 6 with vitamin D3, 2 with bivalent HPV vaccine, and 2 with zinc sulphate. The participant age ranged from 4 to 75 years. The majority of the included trials were conducted in Egypt, with one originating in India. The studies were published between 2019 and 2023. In the studies we included, the most common types of warts were common, genital, plantar, and periungual. The characteristics of studies are shown in **Table I**.

The result of the risk of bias is presented in **Fig. 2**. In most evaluated studies, the RoB 2.0 quality assessments exposed an unclear risk of bias across various domains. Six of the 24 included studies exhibited a high risk of bias in the domains of allocation concealment and random sequence, with no mention of randomization in patient grouping in these studies (15, 18, 22, 24–26). Furthermore, a high risk of bias in the single blinding of results, participants, and/or professionals was identified in 3 out of the 24 included studies (18, 19, 34), raising concerns regarding potential sources of bias in the reported outcomes.

Clinical effectiveness

First, in the complete clearance group (**Fig. 3**), 6 subgroups were established to examine complete clearance. The control groups were saline, MMR, PPD, vitamin D3, bivalent HPV vaccine, and zinc sulphate. Intralesional *Candida* injection therapy showed a significant improvement compared with saline (RR 5.39, 95% CI 3.49–8.33; I^2=0%). However, when compared with MMR (RR 1.07, 95% CI 0.78–1.47; I^2=76%), PPD (RR 1.08, 95% CI 0.90–1.29; I^2=56%), vitamin D3 (RR 1.13, 95% CI 0.75–1.71; I^2=78%), bivalent HPV vaccine (RR 1.36, 95% CI 0.90–2.06; I^2=0%), and zinc sulphate (RR 1.14, 95% CI 0.91–1.45; I^2=0%), no statistically significant differences were found in the complete response rate for wart treatment.

Regarding partial clearance (**Fig. 4**), 6 subgroups were also established, with the control groups being identical to those of the complete clearance group. Intralesional *Candida* injection therapy demonstrated some improvement compared with saline (RR 1.71, 95% CI 0.86–3.41; I^2=54%) and PPD (RR 1.24, 95% CI 0.59–2.59; I^2=72%), although these differences were not statistically significant. Conversely, other therapies showed better partial

Table I. Characteristics of studies meeting inclusion criteria

Study	Country	Arm	Age, years	Lesions (*n*)	Duration of warts, months	Type of warts	No. of immunotherapy sessions	Interval between sessions
Nasr et al., 2023 (23)	Egypt	*Candida*	26.7±5.86	Median 5	8.97±8.27	Common warts, palmoplantar warts, periungual warts, plane warts, filiform warts, genital warts	Maximum 5	Week
		Vitamin D3	29.1±7.53	Median 5	8.4±5.73			
		Digoxin and furosemide	29.5±7.63	Median 5	7.88±4.82			
Fawzy et al., 2023 (19)	Egypt	*Candida*	42.2±13	18±6.96	9.8±8.1	Anogenital warts	Maximum 3	2 weeks
		Candida + Cervarix	41.8±11.9	20.8±8.6	11±8		Maximum 5 (3 of *Candida* and 2 of Cervarix)	1 week
		Candida + Gardasil	32.6±12.8	15.8±10.1	5.2±3.9		Maximum 5 (3 of *Candida* and 2 of Gardasil)	1 week
		Saline	39.4±12.1	15±4.6	7.8±3.9		Maximum 3	2 weeks
Chaudhary et al., 2023 (16)	India	MMR PPD *Candida* Vitamin D3	18–75	Multiple (>5)	A total of 53% of the patients had a disease duration of fewer than 6 months	Cutaneous warts	Maximum 3	3 weeks
Youssef et al., 2023 (35)	Egypt	*Candida* (1/100 concentration)	4–49	20.09±24.12	14.49±13.80	Common warts, plantar warts, plane warts	Maximum 6	2 weeks
		Candida (1/1000 concentration)		19.97±25.63	13.00±13.10			
		Zinc sulphate		22.40± 23.04	15.69±13.14			
Tawfik et al., 2022 (34)	Egypt	PPD	35.77±10.19	18.54±9.78	6.47±6.34	Genital warts	Maximum 4	2 weeks
		Candida	38.68±6.81	15.0±11.07	6.02±4.33			
Nofal et al., 2022[a] (27)	Egypt	*Candida*	18–54	5–50	2–7 (yrs)	Multiple (>5) recalcitrant plantar warts	Maximum 5	2 weeks
		PPD						
		Saline						
Eldahshan et al., 2022 (17)	Egypt	MMR	34.6±9.7	2.6±0.89	2.6±1.28 (yrs)	Extragenital warts	Maximum 5	2 weeks
		BCG	35.7±11.05	2.77±1.07	2.7±1.1 (yrs)			
		Candida	35.2±9.07	2.9±1.06	2.65±1.19 (yrs)			
Nassar et al., 2022[a] (24)	Egypt	*Candida*	30.33±17.88	Multiple	11.2±5.35	Common warts		
		Bivalent HPV vaccine	29.96±18.85		10.7±3.94			
		Cryotherapy	31.73±17.80		10.9±3.89			
		Saline	31.93±17.58		10.5±3.73			
Nassar et al., 2022[b] (26)	Egypt	*Candida*	32.8±12.74	Multiple	-	Common warts	Maximum 5	2 weeks
		Saline	30.76±12.08					
Nofal et al., 2022[b] (28)	Egypt	MMR	6.5±7.77	23.5±13.435	7±5.676	Anogenital warts	Maximum 5	2 weeks
		Candida	6.5±6.36	21.5±9.192	9±7.071			
		Saline	5±5.65	19.5±7.778	6±4.242			
Nofal et al., 2022[c] (30)	Egypt	Zinc sulphate	25.21±11.74	2±1.27	3.63±1.86 (yrs)	Recalcitrant plantar warts	Maximum 4	3 weeks
		Vitamin D3	27.89±12.66	2.89±2.3	3.42±2.12 (yrs)			
		Candida	26.32±11.87	2.5±1.9	3.33±1.92 (yrs)			
		Saline	25.64±12.23	2.2±1.8	3.52±2.03 (yrs)			
Abdel Razik et al., 2021 (13)	Egypt	*Candida*	19.50–35.50	3.0–10.0	17.64±3.0	Common warts	Maximum 4	3 weeks
		Vitamin D3	20.0–30.0	4.0–7.0	17.38±3.29			
		Saline	21.0–29.0	4.0–5.0	16.82±2.74			
Abdelaal et al., 2021(14)	Egypt	Vitamin D3	30.4±8.6	2.2±0.9	4.4±1.6	Plantar warts	Maximum 3	3 weeks
		Candida	31.9±9.7	2.6±1.1	4.3±1.7			
Rageh et al., 2021 (33)	Egypt	*Candida*	31.6±11.3	Single: 6 Multiple: 24	6.66±3.22	Plantar warts	Maximum 5	3 weeks
		MMR vaccine	32.2±11.1	Single: 8 Multiple: 22	10.66±8.89			
Nofal et al., 2021 (29)	Egypt	PPD	11.3±7.64	2.21±1.22	1.88±2.13 (yrs)	Periungual warts	Maximum 5	2 weeks
		Candida	14.8±9.2	3.98±1.77	1.16±1.13 (yrs)			
		MMR	16.5±12.7	4.81±1.32	1.02±1.5 (yrs)			
Amer et al., 2021 (15)	Egypt	*Candida*	26.39±8.58	3–15	1–5 (yrs)	Plantar warts, genital warts, plane warts	Maximum 4	2 weeks
		Varicella zoster vaccine	29.78±9.31					
Hodeib et al., 2021 (20)	Egypt	*Candida*	18.9±7.7	1–5 (*n*): 9 6–10 (*n*): 4 >10 (*n*): 7	–	Plane warts (face, upper limb)	Maximum 4	2 weeks
		Bleomycin	25.1±9.4	1–5 (*n*): 12 6–10 (*n*): 6 >10 (n): 2				
		5 –FU	22.95±10.7	1–5 (*n*): 10 6–10 (*n*): 7 >10 (*n*): 2	–			
Marei et al., 2020[a] (21)	Egypt	*Candida*	50.7±4.9	5–12	2±0.75 (yrs)	Common, plantar, periungual, genital	Maximum 5	2 weeks
		Saline	52.6±3.7	3–10	1.7±0.34 (yrs)			
Nassar et al., 2020 (25)	Egypt	Methylene blue and intense pulsed light	15.8±11.1	23±21.4	3–60	Plane warts	Maximum 3	2 weeks
		Candida	16.5±9.7	18.4±13.1	3–36		Maximum 5	
		Saline	15.8±11.1	19.5±12.4	3–36		Maximum 5	
Fawzy et al., 2020 (5)	Egypt	PPD	12.3±8.65	19.21±3.22	1.88±2.13 (yrs)	Multiple plane warts (face, hand)	Maximum 5	2 weeks
		Candida	14.8±9.2	17.89±5.77	1.16±1.13 (yr)			
		MMR	19.5±11.6	14.81±5.32	1.97±1.02 (yrs)			
Nofal et al., 2020[a] (32)	Egypt	PPD	21.2±9.78	7.05±4.90	1.97±1.02	Common warts	Maximum 6	2 weeks
		Candida	23.9±12.3	9.21±7.67	2.26±1.24			
		Alternating therapy of PPD and *Candida*	22.4±10.7	9.70±8.25	2.5±2.30			
		Saline	22.5±10.1	7.4±4.42	2.3±1.4			
Nofal et al., 2020[b] (31)	Egypt	PPD	24.4±10.7	8.56±7.17	5.5±8.9 (yrs)	Multiple recalcitrant genital warts	Maximum 5	2 weeks
		Candida	30.7±12.5	9.225±8.55	4.9±6.7			
Marei et al., 2020[b] (22)	Egypt	*Candida*	31±12.9	9.8±4.75	2.58±1.12	Recalcitrant warts	Maximum 5	2 weeks
		Combined therapy *Candida* + Cervarix vaccine	29±8.47	11.2±3.62	3.22±2.53			
Fathy et al., 2019 (18)	Egypt	Cholecalciferol (vit D3)	responders/non responders 28.86±6.05 32.00±7.21	10.00±5.48 15.33±9.03	21.14±22.52 53.00±35.68	Multiple recalcitrant warts plantar warts	Maximum 3	3 weeks
		Candida	28.11±4.70 24.55±4.16	8.22±2.86 14.00±7.96	24.11±12.55 37.64±19.73			
		Saline	20–40	–	–			

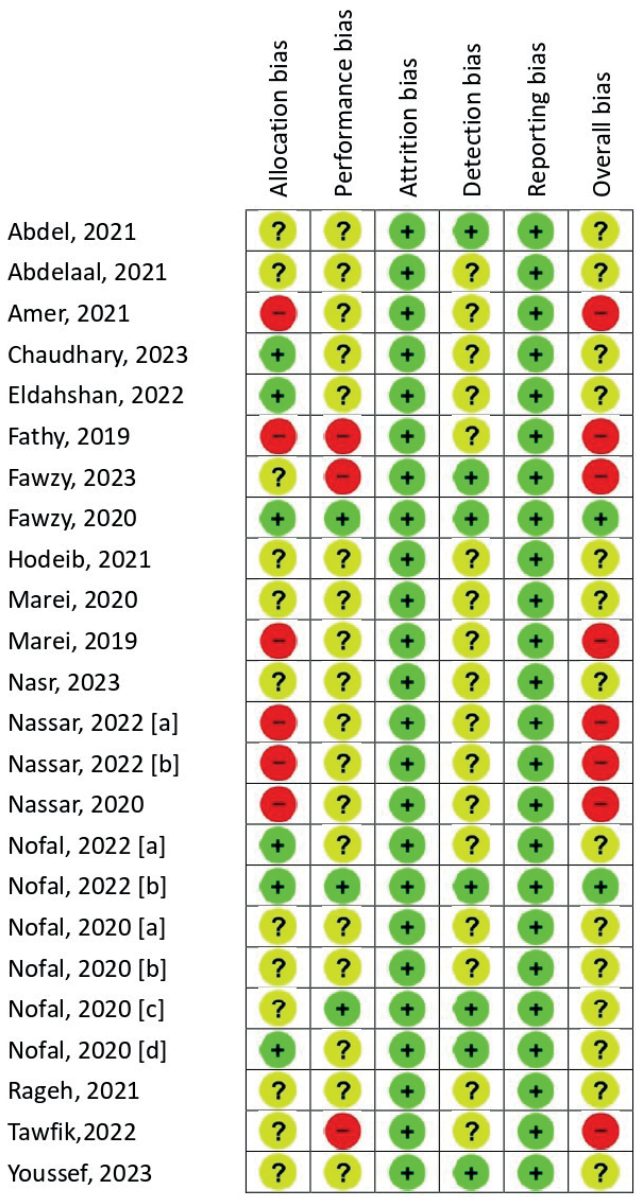

Fig. 2. Risk of bias summary.

response rates when compared with *Candida* injection, including MMR (RR 0.88, 95% CI 0.55–1.39; I^2=0%), vitamin D3 (RR 0.75, 95% CI 0.48–1.16; I^2=0%), bivalent HPV vaccine (RR 0.57, 95% CI 0.32–1.01; I^2=0%), and zinc sulphate (RR 0.85, 95% CI 0.48–1.48; I^2=0%).

Of the studies included in this meta-analysis, 11 provided comprehensive treatment response data for distant warts situated in anatomically different body parts (**Fig. 5**). Intralesional *Candida* injection therapy demonstrated a significant improvement in the rate of distant complete response for wart treatment when compared with both saline (RR 10.54, 95% CI 3.81–29.17; I^2=0%) and bivalent HPV vaccine (RR 1.75, 95% CI 1.06–2.88). Conversely, when compared with MMR (RR 1.06, 95% CI 0.74 –1.50; I^2=47%), PPD (RR 1.20, 95% CI 0.95–1.53; I^2=0%), vitamin D3 (RR 1.98, 95% CI 0.78–5.00; I^2=60%), and zinc sulphate (RR 2.78, 95% CI 0.33–23.63; I^2=65%), no statistically significant differences were found from that of the *Candida* group.

Adverse effects

This analysis encompassed 24 clinical studies, wherein general reported adverse effects of intra-lesional injections were documented. Among these studies, 19 provided specific frequency data for these events. The most commonly observed adverse event was injection-related pain, which was reported in 20 of 24 studies regardless of the intralesional injection agent used. Additionally, flu-like symptoms were noted in 16 of the 24 studies (frequency of 0% to 60%). Other adverse events, such as erythema and swelling, were frequently reported. Rare adverse events included hypopigmentation, injection site blisters, desquamation, vomiting, and severe headache. Although the aforementioned side effects specifically refer to *Candida*, similar symptoms are also observed with other intralesional injections (see Table SIV).

Publication bias

Funnel plots of complete and partial response of *Candida* compared with saline were conducted, respectively. The funnel plot for *Candida*'s partial response versus saline showed symmetry (Fig. S2B). Conversely, the result of complete response of *Candida* compared with saline appeared to be asymmetric. Egger's test for a regression intercept had a p-value of < 0.001, indicating possible publication bias. Owing to the presence of publication bias, trim and fill analysis using a random-effects model was performed to correct for funnel plot asymmetry and adjust for the final pooled estimate (Fig. S2A). Six studies were missing on the left side of the mean effect in complete response to *Candida* compared with the saline group. After inserting 6 imputed studies, the results remained significant with an RR of 4.355 (95% CI 2.582–7.345). Accordingly, potential publication bias does not have a considerable effect on the estimated risk.

Quality of evidence

This meta-analysis explored 3 types of outcomes related to the treatment efficacy of *Candida* antigen. The quality of evidence for outcome measures according to the GRADE system is presented in Tables SV5–SVII. In this review, there were 6 trials with moderate quality of evidence, 9 with low quality of evidence, and 3 with very low evidence quality.

DISCUSSION

The analysis of RCTs revealed that intralesional *Candida* injection was significantly more effective than placebo in

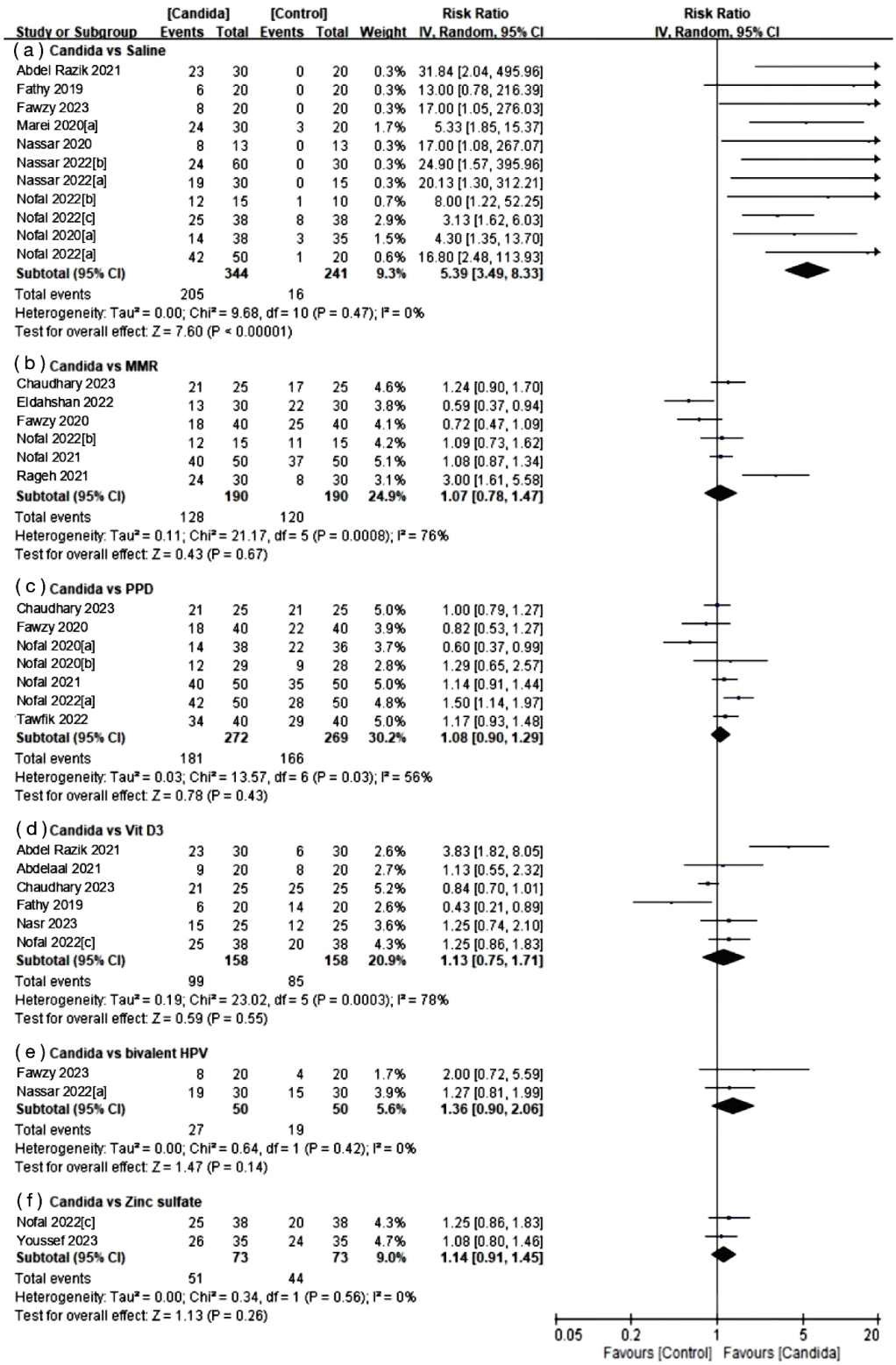

Fig. 3. Forest plots of meta-analysis for complete response rate.

treating warts. Furthermore, we analysed the therapeutic efficacy of intralesional injection agents by reviewing all known RCTs involving *Candida*. The complete response rate for the *Candida* immunotherapeutic agent was slightly higher than that for MMR, PPD, vitamin D3, bivalent HPV vaccine, and zinc sulphate; however, the difference was not statistically significant. Conversely, intralesional *Candida* injection therapy significantly improved distant complete response rates for wart treatment compared with saline and bivalent HPV vaccine.

Immunotherapy is a treatment approach for warts that stimulates a systemic immune response. The precise

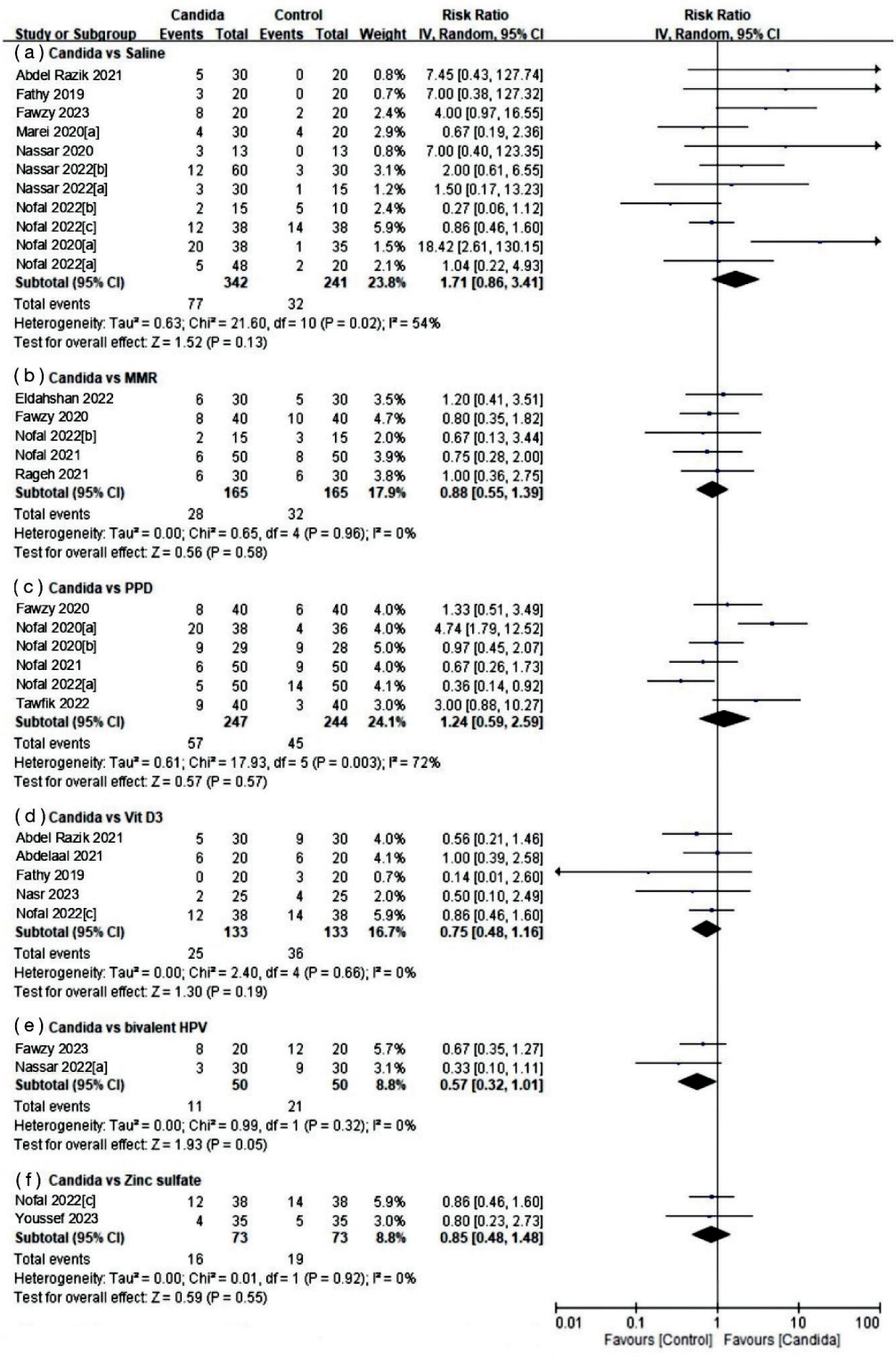

Fig. 4. Forest plots of meta-analysis for partial response rate.

mechanism underlying the effectiveness of intralesional immunotherapy, including *Candida* immunotherapeutic agents, remains unclear but it has been hypothesized that type 1 T helper (Th1) cytokine, tumour necrosis factor alpha (TNF-α), and interferon-γ (INF-γ) production may suppress HPV gene transcription, leading to cytotoxic T cell and natural killer cell activation, ultimately eliminating HPV-infected cells (26, 36). Although intralesional immunotherapy methods may share some common mechanisms of action, immune response between them may be variable. Recently, Nassar et al. (26) reported the roles of Interleukin 17A (IL17A) and migration inhibitory factor (MIF) in the mechanism of action of *Candida* antigen for treating common warts.

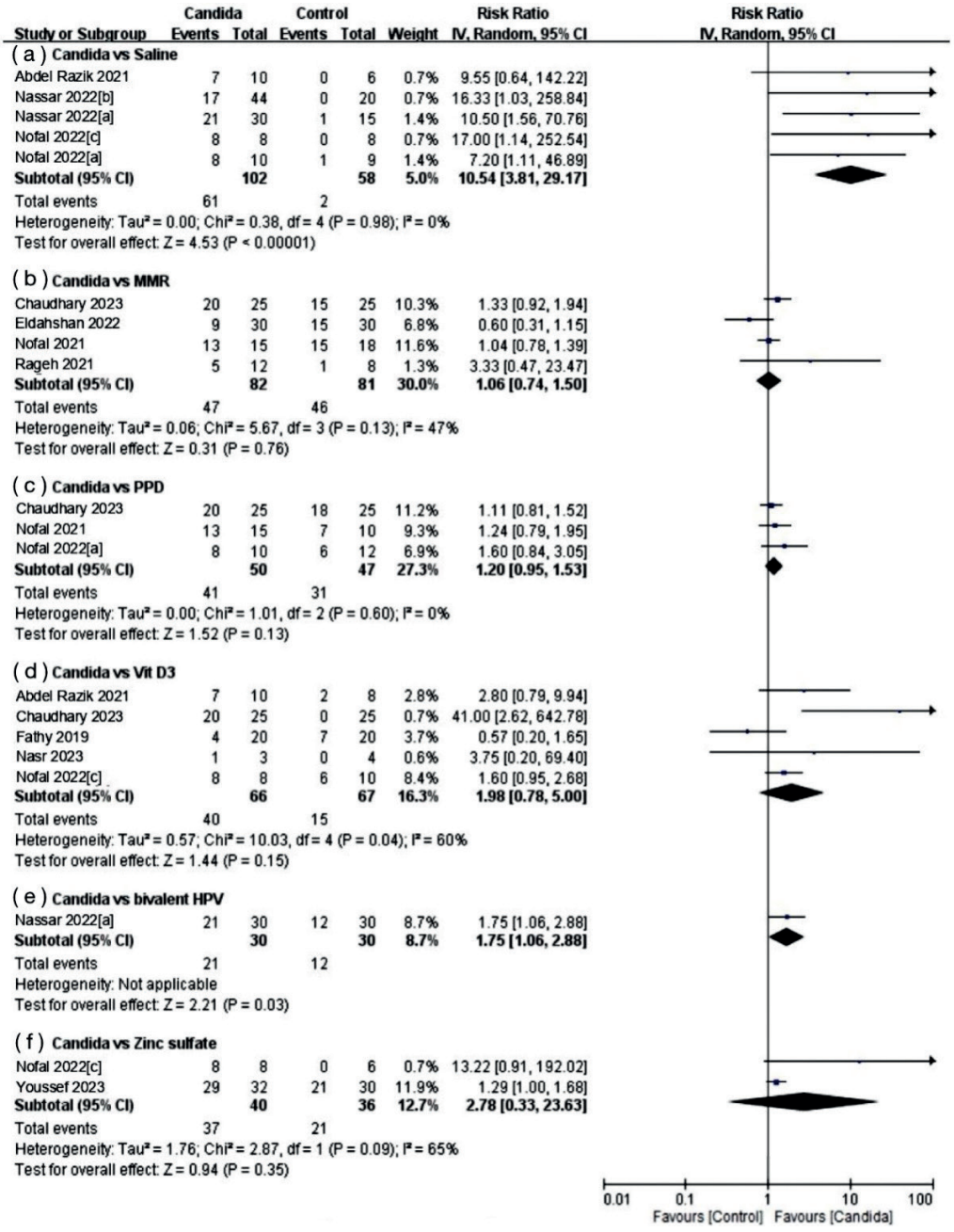

Fig. 5. Forest plots of meta-analysis for distant response rate.

In another study conducted by Sorour et al. (37), a significant increase in the intensity of cathelicidin (LL37) expression was noted following an intralesional vitamin D3 injection for verruca vulgaris, to suggest immune action mechanisms. Although no statistically significant differences were noted in the therapeutic effectiveness among these intralesional immunotherapy agents in our analysis, further research into the specific mechanistic variations of each agent is warranted.

It is important to note that *Candida* antigen comes from different commercial sources, each with varying compositions and manufacturing processes. However, few studies directly compare these sources. Most of the studies we reviewed did not specify how the *Candida* antigen was prepared. Three studies did mention using *Candida* antigen from Allergy Laboratories, Inc. (17, 22, 25), at a concentration of 1:1,000 and a dose of 0.2 mL. This product, made by an FDA-licensed manufacturer, is subject to strict quality control. Differences in antigen formulation could affect immune response and treatment efficacy, highlighting the need for consistent testing procedures to ensure reliable clinical results.

Adverse effects associated with intralesional *Candida* therapy included pain, flu-like symptoms, erythema, and localized oedema at the injection site. The most common reaction is pain at the injection site, which is typically of short duration. Although no severe adverse events were reported in the included studies, a single case report

documented a severe adverse event involving a painful purple digit after injection of *Candida* antigen for periungual wart treatment (38). In summary, the side effects observed did not raise significant safety concerns. Thus, intralesional *Candida* immunotherapy is widely considered as a safe and well-tolerated option, and patients have consistently reported satisfaction with this treatment (35).

The strengths of the review include a rigorous approach of minimizing bias in the study selection and data analysis. We employed systematic search strategies to identify relevant studies, thereby reducing the likelihood of missing critical evidence. Moreover, the review assessed the risk of bias within the included studies, providing transparency in evaluating the quality of the evidence.

This review has several limitations. First, the exclusion of unpublished or non-English studies may affect the overall comprehensiveness of the findings. Second, most of the included studies were done in Egypt and 1 in India, which raises questions regarding the generalizability of treatment efficiency across diverse racial populations. Third, the treatment efficacy of warts is associated with age and sex; however, most of the included studies failed to categorize patients based on these factors, preventing a comprehensive discussion on their potential influence. Fourth, more than half of the studies featured a relatively small sample size, with fewer than 30 participants per treatment group. The limited number of participants may have affected the generalizability of the results. Fifth, the included studies generally lacked assessments of the long-term effects and recurrence rate of intralesional *Candida* injection therapy, typically following patients for up to 6 months. This limited duration suggests that the long-term efficiency is not well known. Lastly, 8 of the 24 included studies showed a high risk of bias overall. These studies had flaws in allocation concealment, random sequence, and blinding of patients and professionals in treatments. A "high risk" rating indicates a significant bias that may invalidate the results. To address these concerns, initiating more robust multicentre RCTs on intralesional *Candida* injection therapy for warts is crucial to prevent bias. Future research should aim for larger and more diverse studies to provide more conclusive evidence.

In summary, our systematic review and meta-analysis underscore the efficacy of intralesional *Candida* injection therapy for cutaneous warts, showing significant advantages over placebo in achieving complete primary and distant warts recovery. Mild and manageable adverse effects support the safety profile of this immunotherapeutic approach. In conclusion, intralesional *Candida* immunotherapy holds promise for warts treatment; however, ongoing research is essential to enhance the understanding of the most appropriate form of *Candida* antigen, and its long-term efficacy and safety.

The authors have no conflicts of interest to declare.

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