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REVIEW ARTICLE

The effects of CO_2 laser and topical agent combination therapy for onychomycosis: A meta-analysis

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Abstract

The routine options for onychomycosis are oral, topical, and device-based therapies which are often limited in terms of efficacy and unsatisfactory side effects. Topical agents such as luliconazole, tioconazole, terbinafine, and tazarotene can be more effective when combined with laser therapies. Our aim was to compare the efficacy and satisfaction rates of CO_2 laser therapy with topical agents in patients with onychomycosis. PubMed, the Cochrane Library, Embase, and Ovid databases were searched to identify randomized controlled trials (RCTs) evaluating the effects of combined therapies. Selected study data were analyzed for differences expressed as odds ratio (*OR*) and relative ratio (*RR*) with 95% confidence intervals (*CI*) for dichotomous outcomes. Efficacy and satisfaction outcomes were assessed using quantitative methods. Our investigations showed that combined CO_2 laser and topical treatments significantly increased efficacy 5.38-fold when compared with topical agents alone (*OR* 5.38; 95% *CI*; 3.20–9.04; $p < 0.00001$), with low heterogeneity observed among studies ($I^2 = 38\%$). Mycological clearance comparison rates were also improved by combined treatments. The higher satisfaction of the combined group was assessed by pooled effect (*OR* 4.56; 95% *CI*; 2.78–7.49; $p < 0.00001$). Our evidence suggests combined therapy may exert positive effects and satisfactory safety for patients with moderate to severe onychomycosis, however, optimal combination options and appropriate dosages require more comprehensive RCTs.

KEYWORDS
CO_2 laser, meta-analysis, mycological clearance, onychomycosis, topical agents

1 | INTRODUCTION

Onychomycosis is a common, chronic nail disease that accounts for 50% of all nail diseases.[1] It is caused by dermatophytes, non-dermatophytes, and yeasts[2] and usually leads to nail discoloration, thickening, and separation from the nailbed.[3] Healing is difficult and recurrence rates are high.[4] Approximately 5.5% of the worlds' population are affected by the disease.[5]

Therapeutic options include oral antifungals, topicals, and device-based treatments. Oral antifungals have higher cure rates and shorter treatment periods than other treatments, but may generate adverse reactions due to a significant risk of liver and kidney toxicity and drug interactions.[6] Topical therapy may be an alternative approach for treating onychomycosis and is based on overcoming limitations associated with systemic administration.[7] However, the poor permeability of topicals leads to low cure rates and long treatment periods.[8] Therefore, device-based treatments are currently underway in the search to improve drug permeation.[9] The CO_2 laser is the oldest of the device-based therapies for onychomycosis. Limited CO_2 laser studies combined with topical agents have been conducted and showed good responses.[10–15] However, relative effectiveness and satisfaction for patients and the safety of CO_2 lasers and topical agents for onychomycosis have not yet been systematically analyzed.

On this basis, we performed a meta-analysis of relevant onychomycosis combinatorial therapies to evaluate the comparative efficacy of onychomycosis using CO_2 lasers and topical agents.

2 | MATERIALS AND METHODS

2.1 | Search strategy and selection criteria

A systematic literature review was conducted on April 30, 2021. The literature search strategy is shown (Table 1). Bibliographies from retrieved articles were also searched to identify additional articles that may have been missed during primary retrieval.

2.2 | Study eligibility

The following trials were included: (i) studies were clinical RCTs; (ii) study subjects were diagnosed with onychomycosis, both clinically (as defined by investigators) and mycologically (as defined by mycological testing); (iii) they included CO_2 laser therapy combined with any topical agent for one group, and CO_2 or topical agent monotherapy (or combined) for another group; and (iv) main study outcomes included improvements in efficacy (clinical response and mycological clearance rate) or satisfaction.

Duplicate studies were excluded. The screening of titles and abstracts of remaining studies was independently performed by two researchers using exclusion criteria (Table S1). Disagreements between reviewers were successfully resolved by consensus. Full-text versions of selected articles were retrieved from publishers.

2.3 | Assessment of bias risk

The methodological quality of selected RCTs was independently assessed by two trained investigators according to Cochrane collaboration's tool. Evaluation results were crosschecked to determine the risk of selection, performance, detection, attrition, and reporting bias.

The Forest plot is a common graphical method depicting pooled-effects and confidence intervals (*CI*). Statistical heterogeneity was indicated by little overlap between studies.

TABLE 1 Electronic search strategy

Database	Search terms
Cochrane library	(CO_2 laser): ti, ab, kw AND (onychomycosis): ti, ab, kw
PubMed	(CO_2 laser [title/abstract]) AND (onychomycosis [title/abstract])
Ovid	(CO_2 laser and onychomycosis). ab
Embase	(CO_2 laser): ti, ab, kw AND onychomycosis: ti, ab, kw

Abbreviations: ab, abstract; kw, keywords; ti, title.

Funnel plots of the relative ratio (*RR*) versus the standard error (*SE*) of log *RR* values were assembled using meta-analysis results, and publication bias determined by a visual inspection of plot asymmetry. Plot points should reflect a distribution trend of approximate symmetry as an inverted funnel form to indicate no publication bias, otherwise, potential publication bias is indicated.

2.4 | Data extraction

For each study, data on the following endpoints were extracted where available: (i) basic information including authors and publication year; (ii) basic characteristics including gender, participant age, drop-outs, intervening measures, dosages, study duration, and side effects; and (iii) outcomes based on different indices (degree of improvement and satisfaction).

2.5 | Definition of main outcomes

Efficacy was assessed based on disease improvement using objective measures, including clinical response, scoring clinical index for onychomycosis (*SCIO*), nail clearance, onychomycosis severity index score (*OSI*), and clinical efficacy rate (*CER*). Complete or significant responses were evaluated as events in each trial. Mycological clearance rate data were also extracted for supplementary analysis. Satisfaction outcomes were evaluated by patient reports or graded by scores. Satisfaction degrees such as "very satisfied," and "satisfied," were also evaluated. Study characteristics such as laser mode and treatment duration were also gathered.

2.6 | Heterogeneity analysis

Study heterogeneity was tested using *I*-squared (I^2). Subgroup analyses were applied to clinical factors that may have led to heterogeneity. A fixed effects model was adopted with the inexistence of heterogeneity ($p > 0.10$, $I^2 \leq 50\%$) which was considered as low heterogeneity according to Cochrane Handbook for Systematic Reviews of Interventions, otherwise turning to randomized effect model.

2.7 | Statistical methods

Data were extracted and imported into Review Manager (ver. 5.3), and a meta-analysis was conducted to calculate treatment effects across trials using a random effects model as described by DerSimonian and Laird. Specifically, treatment effects were calculated as *OR*/*RR* with 95% CI using the Mantel–Haenszel method to estimate between-study variation. Differences with a *p*-value <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Study characteristics

Thirty-eight (38) records with approximately 665 patients were retrieved from databases. Twenty-one (21) duplicates were removed, and nine non-conforming studies were also excluded after title and abstract review. Eight full-text articles were assessed and three excluded due to inapplicable outcomes. The remaining five studies fulfilled inclusion criteria and were included in our analysis (Figure 1).

3.2 | Description of studies

Patient characteristics from the five studies are summarized (Table 2).

The five studies included 497 patients with onychomycosis, from which 33 patients were lost to follow-up for either refusing to take oral antifungal agents, or no subsequent responses. In 253 patients, CO_2 laser treatments were combined with topical agents (tioconazole, luliconazole, tazarotene, clotrimazole, and lidocaine). Independent topical antifungal therapy was evaluated in 161 patients and 50 were treated with CO_2 alone. The duration of treatment varied from 3 to 6 months.

3.3 | Quality assessment of studies

The methodological quality of selected RCT studies is described (Figure S1 and Figure S2). Overall, the section of random sequence generation and allocation concealment was all rated as low risk. An unclear risk of allocation concealment existed in all studies, except for Rajbanshi, 2020, which was rated as high risk. In terms of design factors for this type of trial, Zaki, 2020 and Rajbanshi, 2020 satisfied low risk criteria in the section of blinding of participants and personnel. A high risk of incomplete outcome data existed for Zaki, 2020 and Rajbanshi, 2020 due to a high loss to follow-up. Unreported satisfaction resulted in a reporting bias for Rajbanshi, 2020. The five studies were assessed as medium quality or above.

3.4 | Clinical efficacy

We observed significant study differences in terms of low heterogeneity ($I^2 = 38\%$), therefore a fixed effects model was used to pool estimates (OR 5.38; 95% CI, 3.20–9.04; $p < 0.00001$). The outcome showed that clinical efficacy for CO_2 laser and topical antifungal combined groups was superior to topical agents alone, with statistically significant differences (Figure 2).

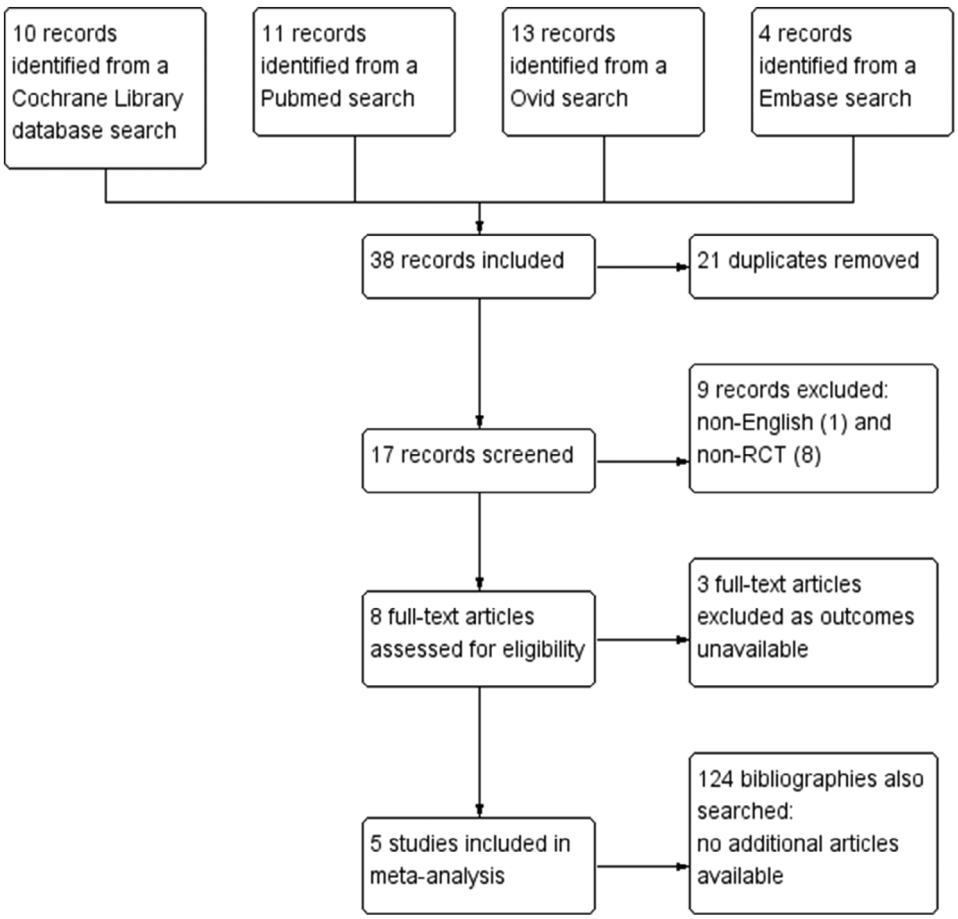

FIGURE 1 Study flow diagram

TABLE 2 General characteristics extracted from five selected clinical studies

Author	Patients	No. of nails	Distribution	Lost to follow-up	Age mean ± SD	Onychomycosis duration	Treatment	Treatment dosage	Duration	Index	Laser mode	Side effects
Zhou, 2016[14]	60 M22/ F38	223 44 fingernails 179 toenails	81 thumb/ big toenails 142 other finger/ toenails	0	37.4 ± 14.25	3 months–18 years	**D**: luliconazole 1% cream **L + D**: CO_2 laser + luliconazole 1% cream	Treated with one pass of fractional CO_2 laser in deep mode at 10–15 mJ, a pulse duration of 0.5–1.0 s, a spot diameter of 4.0–10.0 mm, and a density of 10% over the affected area, including 2–3 mm normal-appearing areas close by. Laser treatment consisted of 12 sessions at 2-week intervals within 6 months.	**L**: 12 sessions at 2-week intervals for 6 months **L + D**: 12 sessions at 2 week intervals combined with cream once daily for 6 months	CER satisfaction	Fractional	Mild pain during laser treatment, No bleeding or oozing during or after treatment
Abd El-Aal, 2019[10]	102 M30/ F72	67% fingernails and 33% toenails	86.2% DLSO 1.9% PSO 9.8% TDO	8	33.17 ± 15.29	A: 1.97 ± 1.31 years B: 4.18 ± 2.41 years	**L + D1**: CO_2 laser + topical tazarotene 0.1% gel **L + D2**: CO_2 laser + topical tioconazole 28% gel	Fractional ablative CO_2 laser 10,600 nm using 10 W, a pulse duration of 500 μs, spacing of 700 and stack 3	**L**: four sessions at 3-week intervals **D**: once a day for 12 weeks	Clinical response	Fractional	—
Zaki, 2020[13]	145 M34/ F86	364	75% DLSO 3.33% PSO 18.3% TDO 3.3% SWO	25	33.97 ± 16.85	2 months–4 years	**L + D**: CO_2 laser + topical tioconazole **L**: CO_2 laser only **D**: topical tioconazole alone	**L**: Power 10–15 W (according to nail thickness), H-Pulse shape, pulse duration of 500 μs, spacing of 700–800 μm and Stack 3 **D**: topical tioconazole 28% solution only twice per day	**L + D**: five sessions with 3-week intervals **L**: five sessions with 3 week intervals **D**: 16 weeks	Clinical response satisfaction	Fractional	—
Rajbanshi, 2020[12]	160 M64/ F96	Fingernail-to-toenail	—	19	43.25 ± 14.34	—	**L + D**: 5% lidocaine	Occlusively applied 5% lidocaine cream 1 h prior using a	Apply the antifungal ointment, terbinafine once a	Nail clearance	Ablative	The laser treatment was tolerated by most patients and

TABLE 2 (Continued)

Author	Patients	No. of nails	Distribution	Lost to follow-up	Age mean ± SD	Onychomycosis duration	Treatment	Treatment dosage	Duration	Index	Laser mode	Side effects
		ratio was 1:3.5					cream + CO_2 laser **D**: antifungal ointment terbinafine	traditional CO_2 laser (10,060 nm)	day on the target nail under occlusion for 1–2 h for 6 months Laser treatment was performed once a month for the first 3 months			no related adverse effects (bleeding, infection) were observed. No complications or side effects in both groups.
El-Tatawy, 2019[15]	30 M4/F26	69	76.67% DLSO 13.33% PSO 10% TDO	0	35.97 ± 8.58	9–72 months	**L**: CO_2 laser **D**: topical tioconazole 28% **L** + **D**: CO_2 laser + topical tioconazole 28%	10.600 nm laser with fluencies in the range of 11–15 W, spacing of 500 μm, dwell time of 500 μs, and stack ranging from 1 to 3. A topical anesthetic cream, 2.5% lidocaine and 2.5% prilocaine was applied 30–60 min before the session.	**L**: six fractional CO_2 laser sessions at monthly intervals **D**: topical tioconazole (28%) nail lacquer twice daily for 6 months **L** + **D**: topical tioconazole (28%) nail lacquer twice daily for 6 months	OSI satisfaction	Fractional	Reported side effects were transient and minimal. Did not affect patient compliance to continue treatment protocols

Abbreviations: CER, clinical response rate; DLSO, distal lateral subungual onychomycosis; D1 and D2, drug 1 and drug 2; EO, endonyx onychomycosis; F, female; M, male; L, laser; OSI, onychomycosis severity index; PSO, proximal subungual onychomycosis; SD, standard deviation; SO, superficial onychomycosis; SWO, superficial white onychomycosis; TDO, total dystrophic onychomycosis.

For a deeper exploration, an efficacy comparison was conducted between the combined group and CO_2 laser treatment alone. The outcome showed that efficacy in the combined group was generally superior to the CO_2 laser treatment alone group, but opposite on small probability (Figure S3).

3.5 | Mycological clearance rate

Mycological examinations were performed in some RCTs using the KOH test. The *RR* value (0.62 and 0.75 in two comparisons) indicated a higher efficacy for combined therapy when compared with sole treatments (Figure S4 and Figure S5).

Also, it was noticeable that the mycological clearance rate of solely treated onychomycosis with CO_2 laser was higher than topical agents (60% vs. 48%), which may suggest a difference in treatment effects.

3.6 | Treatment satisfaction

The reports of "very satisfied" and "satisfied" were counted as outcome data of events in dichotomies. The forest plots of comparisons between combined and sole treatment groups (topical agent or laser alone) were drawn, respectively (Figure 3 and Figure S6).

Patient satisfaction outcomes showed significant differences between the combined group versus topical agent alone group (*OR* 4.56; 95% *CI*, 2.78–7.49; $p < 0.00001$), while no statistical significance was observed between the combined group versus the CO_2 laser treatment alone group ($p = 0.55$).

3.7 | Sensitivity analysis

For this measure, pooled I^2 results did not change greatly by removing any one study, except for Zhou 2016, who used nails as statistical samples instead of patients. As shown (Table S2 and Table S3), the contrast indicated a degree of heterogeneity in this study by counting mode. Other discrepancies in study characters may also be the potential causes, which would be explained in the discussion part, such as duration of treatment.

3.8 | Subgroup analyses

Variable characters in different studies may have impacted on pooled effects. Thus, further subgroup analyses were conducted and results reported with corresponding forest plots.

Different laser modes were categorized into two subgroups (ablative and fractional), with accompanying forest plots (Figure 4). These statistical analyses indicated a higher effect (*OR* = 5.38) in the ablative group. Subgroup difference analyses showed no statistical significances ($p = 0.46$), which indicated similar effects for both ablative CO_2 and fractional CO_2 for onychomycosis.

Different treatment durations were categorized as two subgroups (12 weeks–15 weeks and 24 weeks), with forest plots

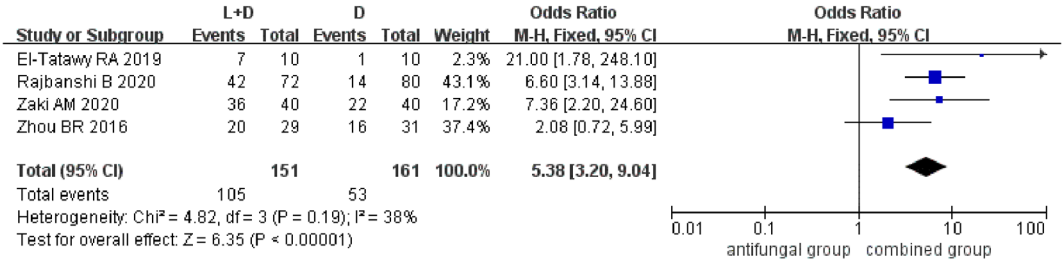

FIGURE 2 Forest plot of comparisons: the combined CO_2 laser and topical agents group versus topical agents alone, outcome: efficacy based on the improvement determined in each study

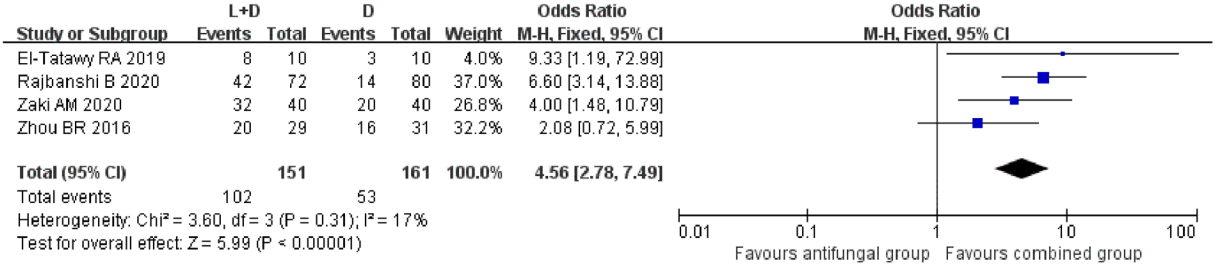

FIGURE 3 Forest plot of comparison: the CO_2 laser and topical agent combined group versus topical agent alone group, outcome: satisfaction based on the degree assessed by patients

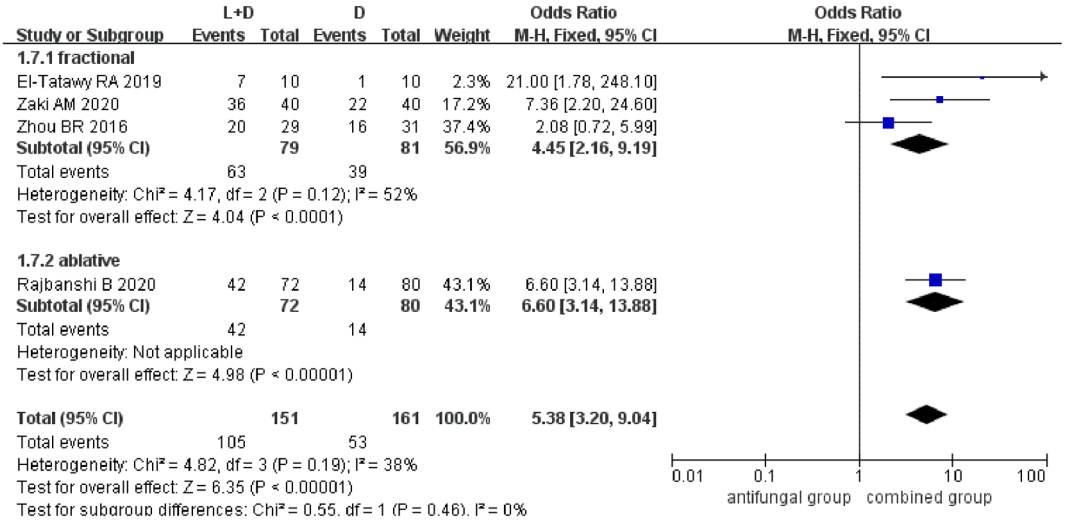

FIGURE 4 Forest plot of comparisons: the fractional CO_2 and antifungal combined group versus antifungals alone, ablative CO_2 and antifungals combined group versus antifungals alone, outcome: efficacy

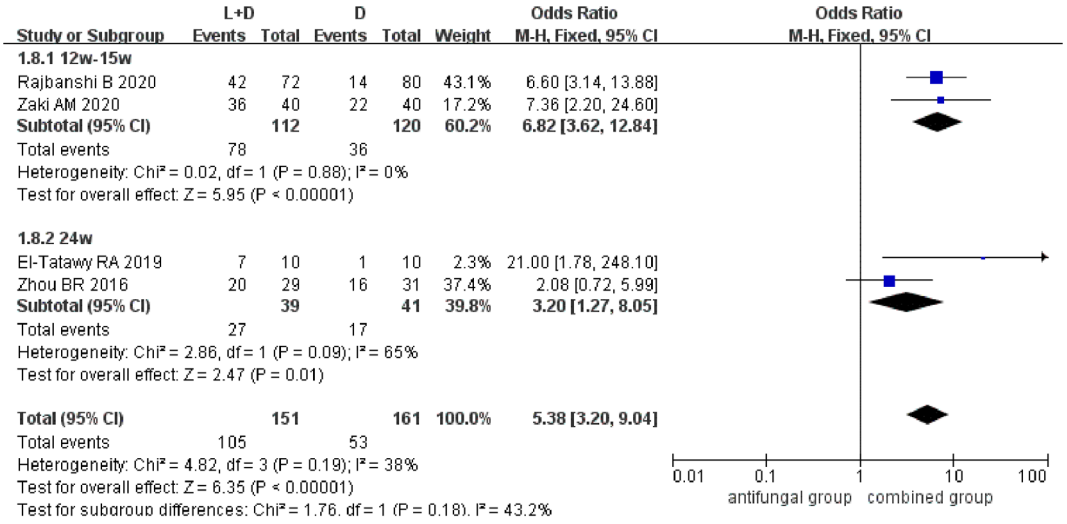

FIGURE 5 Forest plot of comparisons: CO_2 for 12–15 weeks and antifungal combined group versus antifungals alone, CO_2 for 24 weeks and antifungal combined group versus antifungals alone, outcome: efficacy

shown (Figure 5). These statistical analyses indicated a slightly higher clinical efficacy in the 12-15-week group. Subgroup difference analyses showed no statistical significances ($p = 0.18$) which suggested the same treatment duration effects for onychomycosis.

3.9 | Reported adverse events

When compared with antifungal agent groups, few patients reported slight pain in CO_2 laser groups, and transient, minimal effects did not affect patient compliance in the continuance of treatment protocols. However, some patients in the itraconazole-treated group from the study by Chau[11] reported gastrointestinal effects (3), abdominal pain (1) headache (2), and asymptomatic self-limited liver transaminases elevation (2).

3.10 | Publication bias assessment

A funnel plot indicated that points represented a distribution trend of approximate symmetry (Figure 6) with no publication bias observed.

4 | DISCUSSION

This meta-analysis analyzed the efficacy and satisfaction rates of CO_2 laser therapy with topical agents in patients with onychomycosis. We

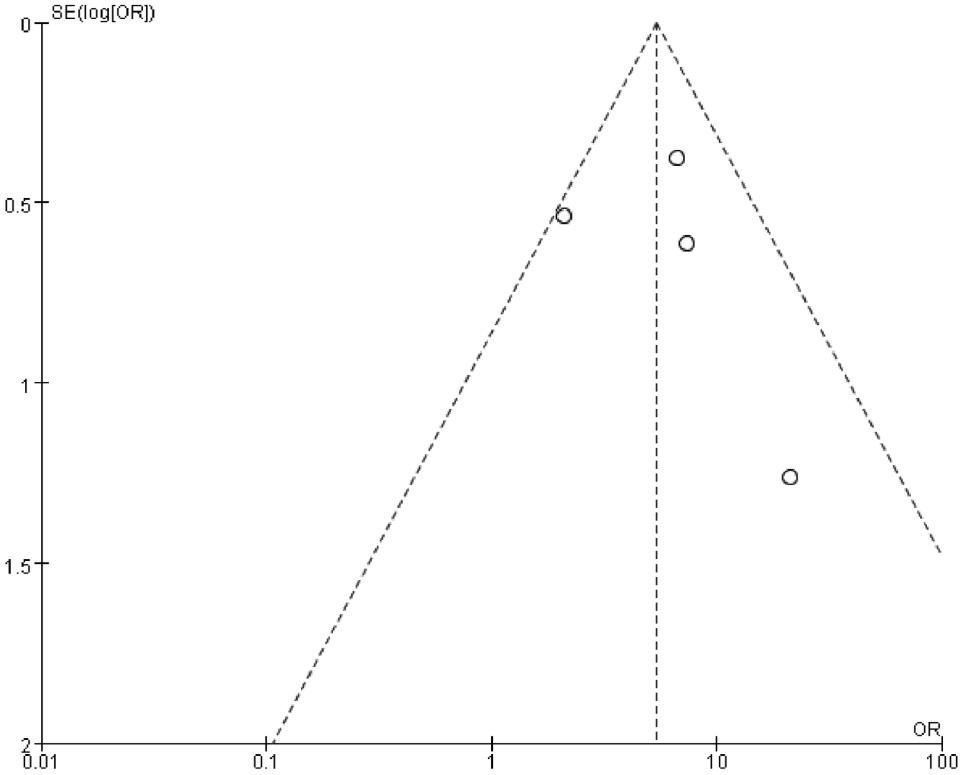

FIGURE 6 Funnel plot of all studies except Abd El-Aal et al. due to unavailable efficacy outcomes

found that combined CO_2 laser therapy and topical agents exhibited significantly higher clinical improvements and mycological clearance rates when compared with topical agents alone. Also, CO_2 laser treatment combined with topical treatments exhibited an improved efficacy when compared with CO_2 laser treatment alone.[13]

CO_2 laser and topical agent combination treatments are widely used to treat onychomycosis. In 2016, Bhatta et al. demonstrated that a fractional CO_2 laser and a topical 1% terbinafine cream approach was effective; 47% of patients exhibited complete responses and 36% exhibited significant responses.[16] Similarly, Šveikauskaitė et al. used fractional CO_2 laser treatment combined with a topical amorolfine cream to effectively treat toenail onychomycosis, with half of patients showing a complete response, with negative mycological examinations and no recurrence within 3 months.[17] The combined therapy approach for onychomycosis may lie in its thermal effects and the assisted delivery of topical drugs. Moreover, fungi are extremely sensitive to temperatures above 55°C; the photothermal effects of fractional CO_2 lasers destroy fungal growth environments, thus contributing to fungal growth inhibition.[15] To systematically evaluate the treatment effect of combined therapy in patients with onychomycosis, we performed this meta-analysis and observed that the combination of CO_2 laser therapy and topical agents exhibited better effects when compared with either monotherapy.

Mycological clearance rate results revealed a priority order of therapeutic effects: combined therapy >CO_2 laser alone >topical agents alone, which indicated that CO_2 lasers were effective treatments for onychomycosis, as a supplementary option.

Satisfaction for combined CO_2 laser and topical agent therapy was superior to the topical agent alone group, which reminded an acceptable treatment. In contrast, comparisons between the combined group and CO_2 laser alone (Figure S6) did not improve satisfaction from topical agents for intolerability.

Sensitivity analyses, based on heterogeneity of efficacy, showed $I^2 = 0$ when Zhou, 2016 was excluded.[14] Heterogeneity may have arisen from statistical analyses investigating the percentage of nails, rather than the percentage of patients. Data reduction might lead to a slight distort on per capita when compared with other trials. For the large size of sample and rigorous design, Zhou, 2016 was not excluded with relatively moderate risk of bias.

We established two subgroups to further explore the impact of laser mode and treatment duration. Comparison results implied no influence on efficacy by intervention, but the leading role of the points above could not have an exact verdict for few comparisons with limited trials. Other subgroups (gender or classification) can be further explored when detailed data are recorded. In addition, we observed that comparison plots between combined and CO_2 laser alone groups (Figure S3) showed a positive effect of antifungal agents, suggesting tioconazole is a good option for clinical treatment. Adverse effects from CO_2 laser treatments were few and acceptable based on selected studies, and thus no quantitative comparisons were required.

Despite no publication bias from our funnel plot data (Figure 6), our meta-analysis had some limitations. Firstly, is a dearth of studies on combinatorial treatments for onychomycosis, with only five RCTs eligible for our research. Limited studies with different topical agents were included in the comparison. Thus, we hypothesize that combination therapy is better than monotherapy. The only conclusion on evidence is tazarotene 0.1% was superior to tioconazole 28% in therapy based on the clinical response and KOH results,[10] but which

antifungal agent of the five included is more preferable still needs more trials to confirm. Secondly, outcomes were comparatively simple and only realistic and rigorous factors were extracted from RCTs, including efficacy, safety, and satisfaction for the complexity and specificity of design in each study. Thirdly, every included trial had not been did not standardized yet to adopt a same treatment course, which may more or less affect the conclusion, although the results we synthesized appeared to be positive.

This systematic review evaluated the current literature on patients with onychomycosis, treated with combined CO_2 laser therapy and topical agents, from treatment efficacy and adverse events perspectives. We showed a combinatorial approach has the potential to be an effective and safe alternative treatment for patients who do not respond to monotherapy, or as a first-line therapy for patients who may benefit from a more aggressive therapy.

5 | CONCLUSIONS

Our meta-analysis suggests that a combined therapy of CO_2 laser treatment and topical agents could exert positive effects and satisfactory safety outcomes in patients with onychomycosis. While treating this condition with CO_2 lasers is a relatively new research field, optimal application methods and other hitherto unknown adverse effects require more RCTs for comprehensive evaluation.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Yang Han analyzed and interpreted data on onychomycosis from all studies and drafted the manuscript. Xiao-dong Li searched the literature and collected data associated with CO_2 laser technology. Yi Wang performed statistical analyses and assessed the risk of bias with Yang Han. Xin-rui Zhang and Juan Chen critically revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript prior to submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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