

Laser treatment for onychomycosis

A systematic review and meta-analysis

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Abstract

Background: Laser systems are a common treatment choice for onychomycosis. They exert their effects on inhibiting the growth of the fungus by selective photothermolysis but efficacy is dependent on the specific type of apparatus used. To systematically review the available published literature on the curative effects and safety of laser treatment for onychomycosis.

Methods: Databases including PubMed, web of science, China National Knowledge Internet (CNKI), WanFang Database and VIP were searched systematically to identify relevant articles published up to July 2018. Potentially relevant articles were sourced, assessed against eligibility criteria by 2 researchers independently and data were extracted from included studies. A meta-analysis was performed using R software.

Results: Thirty-five articles involving 1723 patients and 4278 infected nails were included. Meta-analysis of data extracted from these studies revealed that: the overall mycological cure rate was 63.0% (95%CI 0.53-0.73); the mycological cure rate associated with the 1064-nm Nd: YAG laser was 63.0% (95%CI 0.51-0.74); and that of CO₂ lasers was 74.0% (95%CI 0.37-0.98). The published data indicate that laser treatment is relatively safe, but can cause tolerable pain and occasionally lead to bleeding after treatment.

Conclusion: Laser treatment of onychomycosis is effective and safe. The cumulative cure rate of laser treatment was significantly higher for CO₂ lasers than other types of laser. Laser practitioners should be made aware of potential adverse effects such as pain and bleeding.

Abbreviations: CNKI = china national knowledge internet, RCT = randomized controlled trial, REM = random effects model, MINORS = methodological index for non-randomized studies.

Keywords: laser, Nd-YAG laser, CO₂ laser, onychomycosis, single rate, systematic review

1. Introduction

Onychomycosis is a chronic fungal infection of the nail that may involve the nail bed, plate or matrix. It is difficult to cure and

relapses are common. The condition is caused by dermatophytes, principally *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Candida albicans*.^[1] Clinical classification is performed according to the specific site of infection and includes superficial white onychomycosis, proximal subungual onychomycosis, distal and lateral subungual onychomycosis and total dystrophic onychomycosis. Of these, distal and lateral subungual onychomycosis are the most common.^[2] Traditional treatments for onychomycosis comprise topical, oral, mechanical and chemical therapies.^[3] Topical drug treatments are not usually successful because they are unable to penetrate the nail plate.^[4,5] Oral antifungal agents can produce adverse reactions due to a significant risk of liver and kidney toxicity and drug interactions occurring within the body.^[6] Topical antifungal treatments can be more effective when combined with surgical removal or chemical dissolution of the nail plate.^[7] In 1984, Apfelberg^[8] began using laser treatment for onychomycosis, and since that time laser treatments such as long-pulsed 1064-nm Nd: YAG lasers, short-pulsed 1064-nm Nd: YAG lasers, CO₂ lasers and lasers with wavelengths of 870 nm, 930nm and 1320nm have begun to emerge as new therapies for the treatment of onychomycosis.^[9] Compared with topical and oral therapies, laser treatment offers a more promising therapy for the treatment of the condition in diabetics, elderly patients with drug intolerance, and those with liver and kidney disease.^[10] However, available evidence concerning its efficacy for the treatment of onychomycosis is contradictory.^[11] We therefore conducted a meta-analysis of

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data extracted from available published studies on laser treatment in the context of onychomycosis, in order to evaluate the efficacy and safety of the available different laser devices. It was anticipated that the results would inform and guide future clinical application of laser treatment technologies for onychomycosis.

2. Materials and methods

All data of this study were collected from published trials, so an additional ethical approval is not necessary.

2.1. Search strategy and eligibility criteria

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched electronic databases (PubMed, Web of Science) for studies published up to July 2018 using the Mesh terms “laser, onychomycosis” and “laser, tinea unguium”. We also searched electronic Chinese databases (CNKI, WanFang Database and VIP) for studies published up to July 2018 using the Chinese keywords “laser, onychomycosis,” and “laser and onychomycosis”. The inclusion criteria for the study were as follows:

- (1) Randomized Controlled Trial (RCT) or clinical study in which the onychomycosis group received only laser treatment;
- (2) onychomycosis diagnosed by mycological examination;
- (3) study purpose related to the efficacy of laser treatment for onychomycosis;
- (4) patients had not been treated with systematic antifungal drugs during the preceding 6 months and exhibited no abnormal clinical manifestations associated with other skin diseases such as psoriasis or lichen planus; (4) the treatment group was treated by laser and the control group comprised either a blank control, self-control, and/or laser treatment combined with other treatment options; and
- (5) mycological cure rate and clinical cure rate of diseased nail reported. Since clinical cure rates can vary markedly with different treatments, a meta-analysis of mycological cure rates was performed.

The exclusion criteria were as follows:

- (1) case reports;
- (2) duplicate publications
- (3) conference papers, systematic reviews, and meta-analyses
- (4) studies in which the laser treated group also received other forms of treatment.

2.2. Study selection

Articles were initially assessed by title and abstract only. Those not meeting the inclusion criteria were excluded; duplicate publications were also excluded. Full-text of the remaining articles was retrieved and assessed to determine eligibility for inclusion in the study. Study selection and data extraction were done independently by two reviewers, and the final results were crosschecked. Disagreements were discussed and resolved with consensus or an additional advice was asked to provide by a third reviewer.

2.3. Data extraction

Relevant information was extracted from publications meeting the inclusion/exclusion criteria by the 2 independent researchers. Extracted data included the lead author, year of publication, method of laser treatment, duration of treatment, identified fungi, duration of treatment, number of infected nails, mycological and clinical cure rates in treatment and control groups, duration of follow-up, quality assessment scores (Jadad/methodological index for non-randomized studies (MINORS)).

2.4. Quality assessment

The quality of RCT studies was evaluated according to the Jadad scale,^[12] and the quality of clinical-control articles was evaluated according to the MINORS scale.^[13] In brief, the studies were assessed with respect to the following aspects: randomization, allocation concealment, blinding, baseline comparability, loss to follow-up, grade, and were scored from 0 to 5 (0 being the lowest quality and 5 being the highest quality). The MINORS scale contains 12 items: a clearly stated aim, inclusion of consecutive patients, prospective collection of data, endpoints appropriate to the study aim, unbiased assessment of the study endpoint, appropriate follow-up period, loss to follow-up less than 5%, prospective calculation of required sample size, an adequate control group, contemporary groups, baseline equivalence of patient groups and adequate statistical analyses. Each item is scored from 0 to 2 and the first eight relate specifically to non-randomized studies.

2.5. Statistical analysis

A meta-analysis of the efficacy of laser treatment of onychomycosis was performed using extracted data from included studies. Analyses were conducted using R software combined with the clinical/mycological cure rates and its 95% CI. Chi-squared tests were performed to determine the heterogeneity of the outcome data from the included studies. Subsequent quantitative analyses

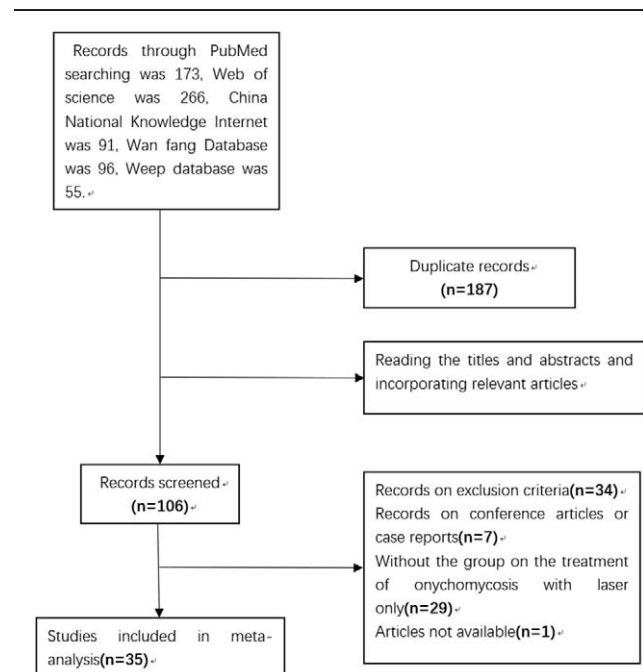


Figure 1. PRISMA flow chart of study identification and selection.

Table 1 Characteristics of studies included in the meta-analysis.

Lead author and reference	Study design	Laser treatment method	Number of treatment episodes	Main fungi/clinical types	No. of patients	No. of infected nails	Mycological cure rate (%)	Clinical cure rate (%)	Follow-up duration (months)	Quality scores (Jadad/MINORS)
Landsman ^[28] (2010)	RCT	870-nm +930-nm laser; energy: 424 J/cm ² ; spot size: 1.5 cm	Four (on day 1, 14, 42 and 120)	DLSO/SWO	34	53	L: 38% C: 15%	L: 8% C: 0%	9	5
Ortiz ^[31] (2014)	RCT	1320-nm Nd: YAG laser; pulse width:350 ms; spot size: 5 mm; frequency: 20 Hz	Four (on day 1, 7, 14 and 60)	—	10	20	L: 50% C: 70%	—	3	4
Hollmig ^[29] (2014)	RCT	The short-pulsed 1064-nm laser; energy: 5 J/cm ² ; pulse width: 0.3 ms; spot size: 6 mm; frequency: 6 Hz	Two with a two week interval	—	22	125	L: 33% C: 20%	L: 2% C: 0%	3	3
Karsai ^[21] (2016)	RCT	The short-pulsed 1064-nm Nd-YAG laser; energy: 20 J/cm ² ; pulse width: 0.1 ms; spot size: 1.5 mm; frequency: 30 Hz	Four with an interval of 4-6 weeks	<i>Trichophyton rubrum</i> /DLSO	20	82	L: 0% C: 0%	OSI: L: 2.0% C: 3.6%	12	3
Zhong ^[32] (2018)	Laser treatment vs. laser + drug treatment	Laser: the short-pulsed 1064-nm Nd-YAG laser; energy: 31.8 J/cm ² ; pulse width: 0.9 ms; spot size: 3 mm spot Laser + drug: oral itraconazole, laser parameters as above	Laser treatment: Eight with an interval of 1 week Oral drugs: 0.2g itraconazole taken orally at meal-times, twice daily for 1 week Three treatment episodes for 7 people, two for 5 people and one for 1 person, with a treatment interval of 4 weeks	SWO, DLSO, PSO, TDO	37 (L: 20; L + D: 17)	178 (L: 83, L + D: 99)	L: 30% L + D: 41.2%	Laser: 31% Laser and drug: 36%	12	16
Kimura ^[24] (2012)	Self-control	The short-pulsed 1064-nm Nd-YAG laser; energy: 14 J/cm ² ; pulse width: 0.3 ms; spot size: 5 mm; frequency: 5 Hz	Three treatment episodes for 7 people, two for 5 people and one for 1 person, with a treatment interval of 4 weeks	DLSO	13	37	51%	81%	4	12
Kim ^[26] (2016)	Laser and drug treatments (comparative study)	Laser: the short-pulsed 1064-nm Nd-YAG laser; energy: 200 J/cm ² ; pulse width: 0.1 ms; spot size: 1.5 mm; frequency: 30 Hz Laser + Drug treatment: laser parameters as above; local treatment with natifine hydrochloride after laser treatment	Laser treatment: Three with an interval of four weeks. If the clinical response was <50% after 12 weeks and the infection continued, one further episode was administered Drugs: Once a day for 24 weeks	<i>Trichophyton rubrum</i>	56 (L:19, L: 19 L + D: 18 D: 19)	217 (L: 79; L + D: 71; D: 67)	L: 15% L + D: 23% D: 5%	L: 32% L + D: 41% D: 8%	6	18
Kalokasidi ^[27] (2013)	Self-control	Q-switched Nd:YAG 1064-nm laser; energy: 5 J/cm ² ; pulse width 0.9 us; spot size: 2.5 mm; frequency: 5 Hz The 532-nm Nd:YAG laser; energy: 14 J/cm ² ; pulse width: 0.9 us; spot size: 2.5 mm; frequency: 5Hz Laser: the long-pulsed 1064-nm Nd-YAG laser; energy: 40-60 J/cm ² ; energy; spot size: 4mm	Two times at intervals of one month (with both lasers).	DLSO	131	131	95.42%	95%	3	11
Okan ^[33] (2017)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 35-40 J/cm ² ; pulse width: 30 ms; spot size: 5 mm; frequency: 1 Hz	Four times at intervals of one week	<i>Trichophyton rubrum</i> /DLSO	15	15	60%	47%	6	11
Zou ^[34] (2014)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 30-40 J/cm ² ; pulse width: 35 ms; spot size: 5 mm	Two to three sessions each of 4 treatments a week, administered at four-week intervals	<i>Trichophyton rubrum</i> /DLSO	33	48	88%	81%	9	13
Lu ^[35] (2013)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 30-40 J/cm ² ; pulse width: 35 ms; spot size: 5 mm	Stage 1: once a week for four weeks Stage 2: once a month for six months	<i>Trichophyton rubrum</i>	35	79	73%	67%	9	11
Li ^[36] (2015)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 45-50 J/cm ² ; spot size: 7 mm; pulse width: 30-40 ms; frequency: 1-10 Hz	Once a week for either 4 weeks (24 patients) or 8 weeks (19 patients)	<i>Trichophyton rubrum</i> /DLSO	43	138	63%	50%	3	11
Yu ^[37] (2017)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 40-60 J/cm ² ; pulse width: 45 ms; spot size: 3 mm; frequency: 2 Hz	Once a week for 8-12 weeks	—	76	287	87%	73%	12	11
Fan ^[38] (2013)	Self-control	—	Once a week for 4 weeks	—	47	76	83%	93%	3	11

(continued)

Table 1
(continued).

Lead author and reference	Study design	Laser treatment method	Number of treatment episodes	Main fungi/clinical types	No. of patients	No. of infected nails	Mycological cure rate (%)	Clinical cure rate (%)	Follow-up duration (months)	Quality scores (Jataad/MINORS)
Yang ^[38] (2016)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 30-40 J/cm ² ; pulse width: 2-35 ms; spot size: 4 mm; frequency: 1 Hz The long-pulsed 1064-nm Nd-YAG laser; energy: 40-60 J/cm ² ; pulse width: 2-35 ms; spot size: 4 mm; frequency: 1 Hz	Once a week for 10-12 weeks	—	104	461	90%	73%	12	12
Moon ^[40] (2014)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 5 J/cm ² ; pulse width: 0.3 ms; spot size: 6 mm; frequency: 5 Hz	Five at four-week intervals	<i>Trichophyton rubrum</i>	13	43 (toenails: 31; fingernails: 12)	70%	28%	1	11
Wanipahakleedecha ^[19] (2015)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 35-45 J/cm ² ; pulse width: 30-35 ms; spot size: 4 mm; frequency: 1 Hz	Four at intervals of 1 month (a second treatment was performed if the fungus was positive at any follow-up visit)	<i>Acremonium bisporus</i> , <i>Trichophyton mentagrophytes</i>	35	52	52%	—	6	12
Kozarey ^[41] (2010)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; energy: 35-40 J/cm ² ; pulse width: 35 ms; spot size: 4 mm; frequency: 1 Hz	Four at intervals of 1 week	DLSO/ <i>Trichophyton rubrum</i>	72	194	100%	—	12	18
Min ^[42] (2016)	Self-control	The long-pulsed 1064-nm Nd-YAG laser; A) energy: 16 J/cm ² ; pulse width: 0.3 ms; spot size: 5 mm; frequency: 10 Hz B) energy: 225 J/cm ² ; pulse width: 0.6 ms; spot size: 2 mm; frequency: 5 Hz	Eight at intervals of 1 week	—	13	40	28%	A: 57% B: 37% Total: 47%	6	12
Xu ^[43] (2012)	Laser treatment, drug treatment, laser + drug treatment (comparative study)	Laser: the long-pulsed 1064-nm Nd-YAG laser; energy: 50-80 J/cm ² ; spot size: 6 mm; pulse width: 12 ms Laser + Drug treatment: laser conditions as above, Nefifen hydrochloride was administered externally after laser treatment	Laser treatment: once a week for 6 months or until fungal cure Drugs: 250 mg Terbinafine orally daily	—	43 (L:15; L+D:16; D:12)	90 (L:31; L+D:29; D:30)	L: 77% L+D: 100% D: 83%	L: 65% L+D: 97% D: 7 3%	6	17
Yao ^[44] (2015)	laser treatment vs. laser + drug treatment	D) oral terbinafine Laser: the long-pulsed 1064-nm Nd-YAG laser; energy: 5-12 J/cm ² ; spot size: 6 mm; pulse width: 0.8 ms; frequency: 5 Hz Laser + Drug treatment: laser conditions as above, compound tincture of golden larch bark was administered externally twice daily	Laser treatment: once a week for 12 weeks Drugs: twice daily for 12 weeks	SWO DLSO, PSO TDO	60 (L:28; L+D:32)	128 (L:62; L+D:66)	L: 29% L+D: 41%	L: 35% L+D: 53%	9	16
Liu ^[45] (2015)	laser treatment vs. drug treatment	Laser: the long-pulsed 1064-nm Nd-YAG laser; spot size: 4 mm; pulse width: 35 ms; energy: 35-80 J/cm ² ; frequency: 1 Hz Drug: 5% amorolfine	Laser treatment: two sessions of each of four treatments administered once a week, with session intervals of 4 weeks Drugs: twice a week for 12 weeks	—	31 (L:22; D:9)	96 (L:63; D:33)	L: 41% D: 61%	L: 41% D: 51%	6	18
Xu ^[46] (2014)	laser treatment vs. drug treatment	Laser: the long-pulsed 1064-nm Nd-YAG laser; energy: 5-15 J/cm ² ; spot size: 3 mm; pulse width: 0.3-2 ms; frequency: 1-10 Hz Drug: 200 mg itraconazole capsule, twice daily Laser: the long-pulsed 1064-nm Nd-YAG laser; energy: 30-40 J/cm ² ; spot size: 4 mm; pulse width: 35 ms; frequency: 1-2 Hz Drug: itraconazole orally with intermittent impact therapy	Laser treatment: four at intervals of one week D: 200 mg Itraconazole twice daily for 4 weeks Laser treatment: once a week for six weeks Drugs: 0.2g itraconazole orally, twice a day for 7 days. Treatment course repeated once for fingernails and twice for toenails.	<i>Trichophyton rubrum</i> , <i>Candida albicans</i>	60 (L:30; D:30)	125 (L:57; D:68)	L: 16% D: 18%	L: 53% D: 68%	6	17
Xu ^[47] (2014)	laser treatment vs. drug treatment	Laser: the long-pulsed 1064-nm Nd-YAG laser; energy: 30-40 J/cm ² ; spot size: 4 mm; pulse width: 35 ms; frequency: 1-2 Hz Drug: itraconazole orally with intermittent impact therapy	Laser treatment: once a week for eight weeks	L: DLSO D: TDO	35 (L: 32; D:32)	64 (L:32; D:32)	L: 78% D: 72%	—	6	16
Chai ^[48] (2017)	laser treatment vs. drug treatment	Laser: the long-pulsed 1064-nm Nd-YAG laser; energy: 30-50 J/cm ² ; spot size: 4 mm; pulse	Laser treatment: once a week for eight weeks	<i>Trichophyton rubrum</i>	—	—	L: 64% D: 67%	—	6	18

(continued)

Table 1
(continued).

Lead author and reference	Study design	Laser treatment method	Number of treatment episodes	Main fungi/clinical types	No. of patients	No. of infected nails	Mycological cure rate (%)	Clinical cure rate (%)	Follow-up duration (months)	Quality scores (Jadad/MINORS)
Liu ^[8] (2014)	laser treatment vs. drug treatment	width: 35 ms; frequency: 1 Hz Drug: 5% amorolfine orally Laser: the long-pulsed 1064-nm Nd:YAG laser; energy: 50-60 J/cm ² ; spot size: 2 mm; pulse width: 35 ms; frequency: 1.5 Hz Drug: oral terbinafine	Drugs: amorolfine twice a week for four weeks, repeated 6 times Laser treatment: once a week for eight weeks Drugs: 200 mg Terbinafine orally twice a day (after meals) for seven days Once a week for eight weeks	—	44 (L:22; D:22) 76 (L:37; D:39)	93 (L:42; D:51) 230 (L:112; D:118)	L: 80% D: 77%	—	6	16
Hu ^[50] (2017)	Laser treatment vs. laser + drug treatment	Laser: the long-pulsed 1064-nm Nd:YAG laser; energy: 30-40 J/cm ² ; spot size: 4 mm; pulse width: 35 ms; frequency: 1 Hz Laser + Drug: Encapsulated with 20% urea for 2-4 h, administered via a burr hole and then treated with the long-pulsed 1064-nm Nd:YAG laser (parameters as above)	Once a week for eight weeks	TDO	61 (L:30; L + D: 31)	101 (L:49; L + D: 52)	L: 57% L + D: 79%	—	6	17
Chen ^[30] (2015)	Laser treatment vs. laser + drug treatment	Laser: the long-pulsed 1064-nm Nd:YAG laser; energy: 70-100 J/cm ² ; spot size: 2 - 6 mm; pulse width: 15-45 ms Laser + Drug: encapsulated with salicylic acid for 48 h, and then treated with the long-pulsed 1064-nm Nd:YAG laser (parameters as above)	Once a week for four weeks and then once a month for six months	—	66 (L:32; L + D:34)	140 (L:72; L + D:68)	L: 72% L + D: 82%	L: 49% L + D: 71%	9	17
Chen ^[51] (2016)	Laser treatment vs. laser + drug treatment	Laser: the long-pulsed 1064-nm Nd:YAG laser; energy: 100 J/cm ² ; spot size: 3 mm; pulse width: 45 ms Laser + Drug: the long-pulsed 1064-nm Nd:YAG laser (parameters as above), followed by topical application of benzoic acid cream	Once a week for twelve weeks	—	132 (L:64; L + D:68)	280 (L:144; L + D:136)	L: 49% L + D: 73%	—	9	18
Song ^[52] (2015)	laser + drug treatment vs. laser treatment	Laser: the long-pulsed 1064-nm Nd:YAG laser; energy: 35 J/cm ² ; spot size: 3 - 4 mm; pulse width: 40 ms; frequency: 1 Hz Laser + Drug: the long-pulsed 1064-nm Nd:YAG laser (parameters as above), followed by topical application of 5% amorolfine cream	Once a week for eight weeks	SWO, DLSO PSO	47 (L:22; L + D:25)	70 (L:33; L + D:37)	70% 76%	67% 73%	3	17
Wang ^[4] (2017)	Laser treatment vs. Nail filing + laser treatment	Laser: the long-pulsed 1064-nm Nd:YAG laser; energy: 45-40 J/cm ² ; spot size: 7mm; pulse width: 30 - 40 ms; frequency: 1 - 10 Hz Nail filing + Laser: Diseased nails ground to a thickness of 0.03-0.05mm, then treated with laser (parameters as above)	Once a week for eight weeks	Dermatophytes	79 (L:37; Nail filing + L:42)	184 (L:85; Nail filing + L:99)	51% 67%	55% 71%	6	18
Yang ^[22] (2015)	Self-control	Laser: ultrapulse CO ₂ dot matrix laser; energy: 5 J/cm ² energy; spot size: 3.0 mm; pulse width: 1 s	Stage 1: once a week for four weeks Stage 2: once every two weeks for eight weeks Once every two weeks until cured	DLSO/ <i>Trichophyton rubrum</i>	18	71	62%	52%	3	12
Liu ^[53] (2008)	Self-control	Laser: CO ₂ cauterization drilling laser; power: 10 - 25 W; spot size: 0.4 mm; pulse width: 0.01 - 0.99 s	Once every two weeks until cured	DLSO, SWO	26	60	100%	90%	6	9
Zhou ^[29] (2016)	RCT	Laser: CO ₂ fractional laser; energy: 10 mJ; spot size: 4.0 - 10.00 mm Drug: 1% luliconazole	Laser treatment: once every two weeks for six months Drugs: once a day for six months	<i>Trichophyton rubrum</i>	60	223	L: 39% L + D: 57%	L: 53% L + D: 73%	6	5
Cheng ^[15] (1997)	Self-control	Laser: CO ₂ laser; energy: 30 W; voltage: 100V; current: 1 - 2 mA; wavelength: 10.6 μm	Once only	—	—	47	83.0%	—	6	9

Notes: C = control, D = drug, DLSO = distal lateral subtype, L = laser, MINORS = methodological index for non-randomized studies, PSO = proximal subty, RCT = randomized controlled trial, SWO = white superficial, TDO = full nail destruction.

of heterogeneity were performed by calculation of I-squared values; where $P < .1$ and/or $I^2 > 50\%$, heterogeneity existed between the data and the combined analysis was performed using a random effects model. Otherwise, a fixed effect model was used. In the subgroup analysis, the chi-squared test was used to identify differences between subgroups. The potential for publication bias was assessed by construction of a funnel plot. Publication bias was considered likely to exist where $P < .05$.

3. Results

3.1. Characteristics of the included studies

The systematic search of the literature identified 681 potentially relevant articles. After removing duplicate publications, 104 articles remained and were subjected to preliminary screening of abstracts (Fig. 1). Following the exclusion of descriptive studies and studies that included other therapies in addition to laser treatment, 35 articles remained that met the eligibility criteria. These 35 articles involved 1723 patients and 4278 diseased nails. The specific data extracted from each of these articles are shown in Table 1. The studies included 5 RCTs. The quality assessment results of the 35 included studies according to the Jadad and MINORS quality evaluation criteria are also presented in Table 1.

3.2. Meta-analysis of extracted data on laser treatment of onychomycosis

The results of the meta-analysis are shown in Figure 2. All 35 included studies reported the efficacy of laser treatment on

onychomycosis. There was statistical heterogeneity among the data from the different studies ($P < .01$, $I^2 > 50\%$), so the random effects model (REM) was used for data analysis. The results of this analysis revealed that the overall mycological cure rate of laser treatment was 63.0% (95% CI 0.53-0.73), as shown in Figure 2. The percentage cure rates of the various subtypes of laser treatment methodology employed in the included studies are shown in Figure 3. The mycological cure rate of long pulse width 1064-nm Nd:YAG laser treatment was 71.0% (95% CI 0.62-0.80); the mycological cure rate of short pulse width 1064-nm Nd:YAG laser treatment was 21.0% (95% CI 0.05 - 0.44); the mycological cure rate of CO₂ fractional laser treatment was 45.0% (95% CI 0.32-0.58); and the mycological cure rate of perforated CO₂ laser treatment was 95.0% (95% CI 0.67-1.00).

3.3. Adverse effects

Among the 35 included studies, 1 reported that the affected nails were filed to a thickness of 0.03 to 0.05 mm prior to laser treatment. In one study, subsequent hemorrhage occurred after treatment and subsided after 2 weeks.^[14] After reducing the laser energy density, there was no evidence of bleeding.^[14] Laser treatment with CO₂ resulted in a larger wound on the nail deck and nail bed and the formation brown eschar, which can readily hemorrhage.^[15] The majority of patients in the included studies reported experiencing a mild to moderate burning sensation during laser treatment, which was tolerable. There were no serious adverse reactions.

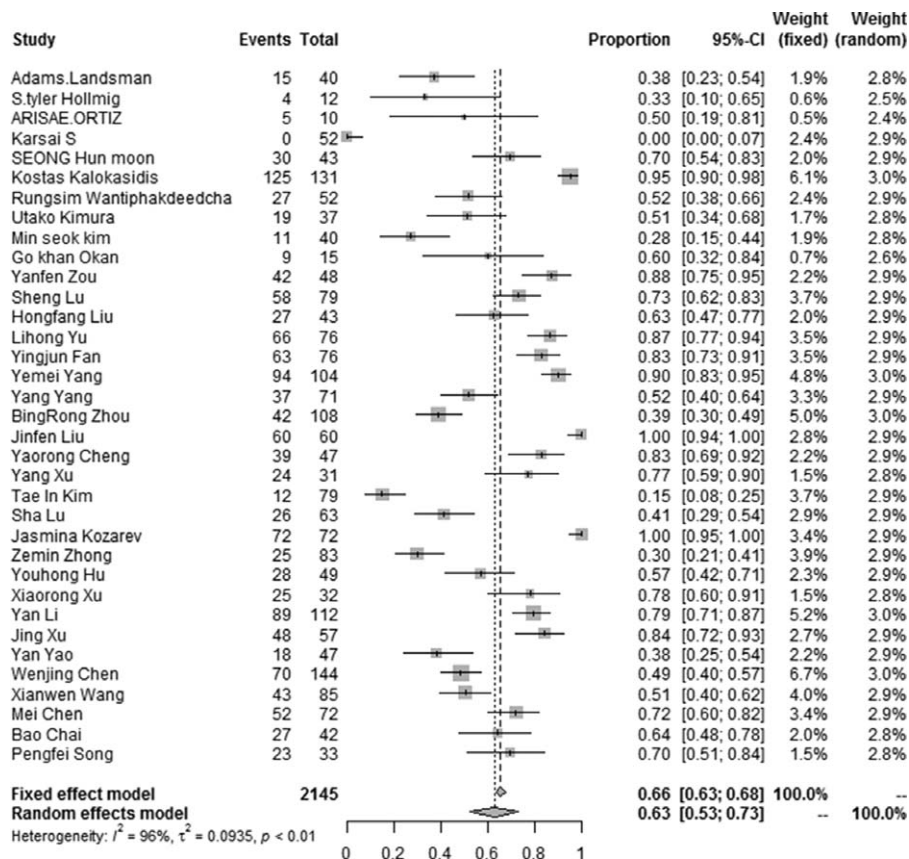


Figure 2. Results (forest plot) of meta-analysis of data extracted from studies on the efficacy of laser treatment for curing onychomycosis.

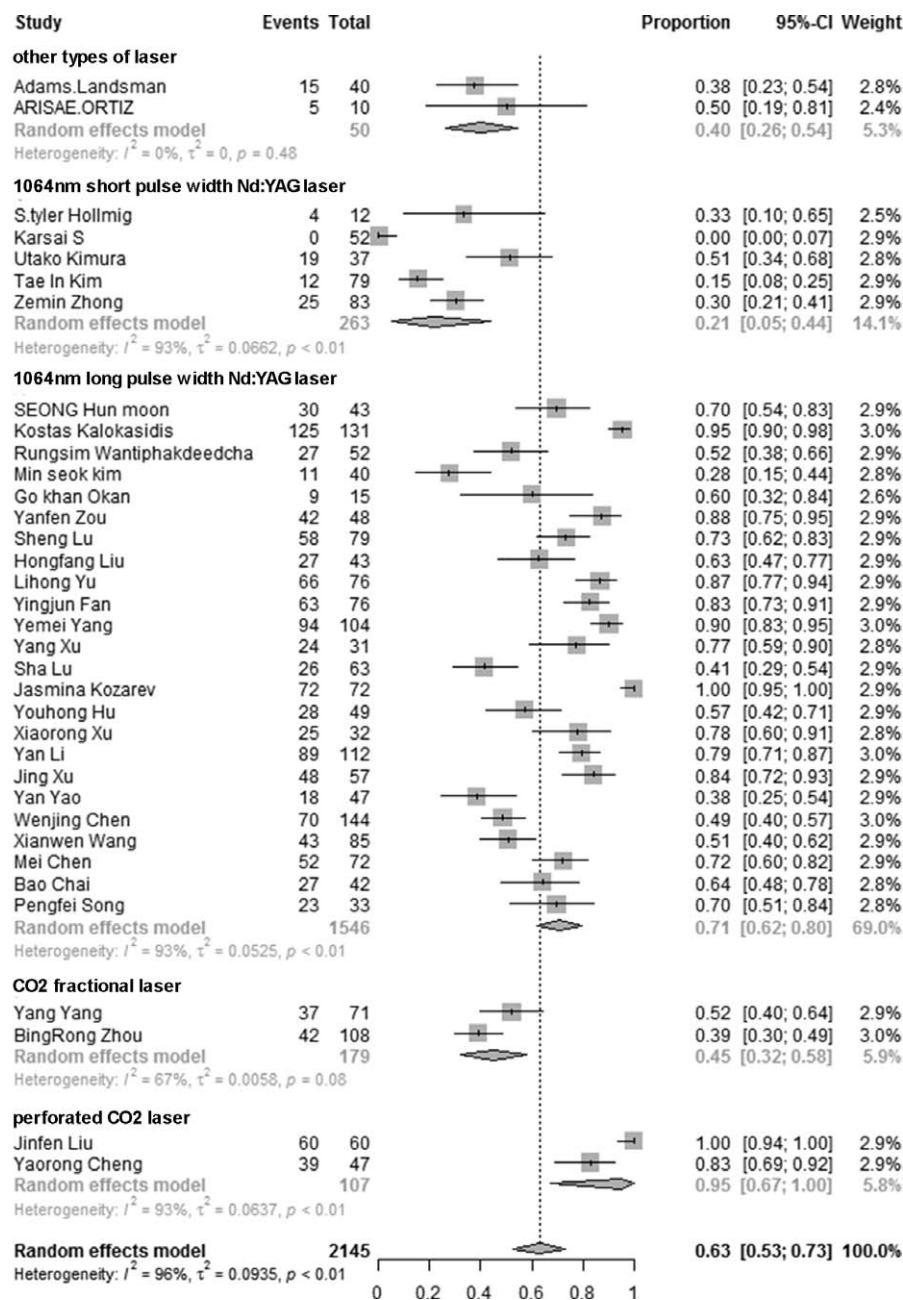


Figure 3. Comparison of the percentage cure rates of different types of laser treatment: 1064-nm Nd: YAG laser (long pulse and short pulse) treatment, CO₂ laser treatment (fractional and perforated) with 870-nm and 930-nm lasers, and other types of laser treatment.

3.4. Publication bias

The constructed funnel plot is presented in Figure 4. There was no evidence of obvious publication bias among the included studies.

4. Discussion:

The meta-analysis performed in this study was conducted on data extracted from 35 articles, including 5 RCT studies, 1723 patients and 4278 diseased nails. The included studies did not show evidence of publication bias and the risk of selective reporting was determined as being low. The majority of the included studies were scored as being of medium quality or above. In general, the analysis revealed that the efficacy of laser

treatment of onychomycosis was approximately 63%. In comparison, the mycological efficacy of itraconazole pulse therapy and continuous terbinafine therapy for the treatment of onychomycosis were 79.6% and 84.8%, respectively.^[16] Thus, the overall efficacy of laser treatment was moderately lower than that of conventional oral drug treatments, but it produced less reported side effects, such as damage to the liver and kidney or gastrointestinal reactions.^[17] Further, the data suggested that laser treatment appeared to be more suitable for certain population subgroups, such as children, the elderly and pregnant women.

The efficacy of CO₂ laser-treatment was found to be slightly higher than that of 1064-nm Nd: YAG laser treatment for curing

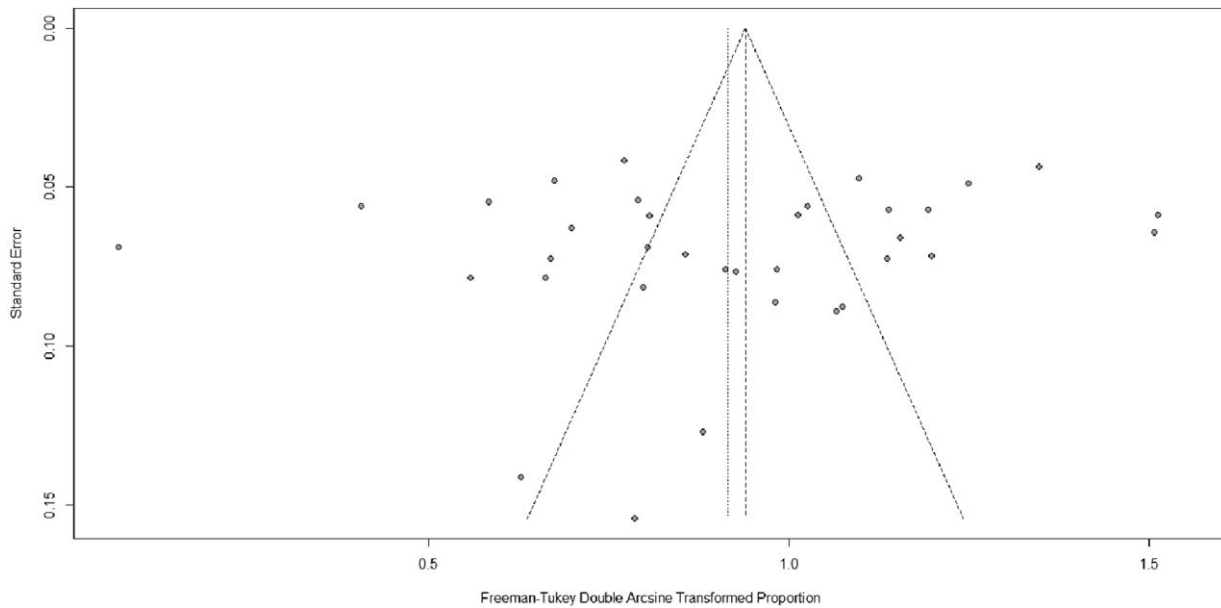


Figure 4. Funnel plot of studies evaluating the effects of laser treatment on onychomycosis, to assess publication bias.

onychomycosis. This may be because whilst the 1064-nm laser inhibits the growth of the fungus, the CO₂ laser can increase the localized temperature and gasify and decompose the infected tissue and have a sterilizing effect.^[18] However, differences between the number of included cases within each of these treatment groups may have influenced the result. The long-pulsed 1064-nm Nd:YAG laser exhibited better efficacy than the short-pulsed 1064-nm Nd:YAG laser. Rungsima et al considered the long-pulsed 1064-nm laser to be more easily absorbed by melanocytes, giving rise to better therapeutic results.^[19] The cytoderm of *Trichophyton* fungi contains a large amount of melanin, and the absorption spectrum of its chromophore is 1064 nm. This means that the long-pulsed 1064-nm Nd:YAG laser can act directly on the chromophore, resulting in a localized increase in temperature and subsequent destruction of the fungi. On the other hand, the short-pulsed 1064-nm Nd:YAG laser acts on the diseased nail, causing tiny bubbles to form and producing sonic shock waves which can significantly inhibit the growth of the fungal colony.^[20] Karsai et al reported that short-pulsed 1064-nm Nd:YAG laser treatment had no effect on either the mycological cure rate or on clinical improvement of onychomycosis caused by *T. rubrum*. It may be that the longer follow-up period of the RCT study (12 months) led to a relatively high recurrence rate or that there was a decrease in the number of potential target chromophores which affected (reduced) the laser-tissue interaction.^[21]

The present analysis also revealed that the efficacy of CO₂ perforated laser treatment was superior to that of CO₂ fractional laser treatment in curing onychomycosis. Among the analyzed studies, the cure rate produced by CO₂ fractional laser treatment was 45%, while the cure rate of CO₂ perforated laser treatment was 95%. Further, the bacteriostatic and sterilizing effects of CO₂ laser treatment did not appear to produce the types of side effects reported for the conventional oral drug therapies. On this basis, Yang et al considered that the efficacy of fractional CO₂ laser treatment could be improved by extending the duration of treatment.^[22] Because of its photothermal effect, perforated CO₂

laser treatment can gasify and entirely decompose the infected tissue, which is likely to achieve a better long-term effect due to improved sterilization. However, compared to CO₂ fractional laser treatment, CO₂ perforated laser treatment produces a higher localized temperature, which can be difficult to control in terms of the depth of laser penetration into the tissue, and which can therefore result in larger wounds, forming a brown eschar and higher risk of bleeding. It is therefore necessary to avoid excessive pursuit of curative effects where the treatment itself may cause excessive clinical damage of the nail bed and deck.

The efficacy of laser treatment in curing onychomycosis depends significantly on the health condition of the patient and on the course of treatment being completed. Carney et al showed that grinding of the diseased nail before treatment in order to achieve a thickness of less than 2 mm was conducive to laser penetration.^[23] Where more than 50% of the diseased nail is affected, malnutrition of the nail and/or invasion of the nail matrix have a detrimental effect on the prognosis following laser treatment. In all except five of the included articles,^[15,24,25,26,27] the laser treatment was repeated at least 4 times. It is therefore considered that changing the treatment duration and the total length of the treatment course could improve the mycological cure rate and clinical efficacy of laser treatment of onychomycosis. In addition to the 1064-nm Nd:YAG laser and CO₂ laser, Landsman et al used 870-nm and a 930-nm lasers to treat severe onychomycosis and this produced a mycological cure rate of only 38%.^[28] Ortiz et al used a 1320-nm Nd:YAG laser to treat onychomycosis but reported that this produced a lower curative efficacy than the control group.^[17] For this reason, 1064-nm Nd:YAG lasers and CO₂ lasers are more commonly used than 1320-nm Nd:YAG lasers. It is worth noting that many studies found that the mycological and clinical efficacy of laser treatment combined with topical drugs was significantly higher than that produced by laser treatment alone,^[29,30] which may be related to the effects of laser treatment in enabling the drugs to penetrate deeper into the nail deck. Yang et al similarly reported that the combination of oral drug therapy and laser treatment was more

effective than administering laser treatment or drug therapy alone.^[30]

The results of the present study have certain limitations: The methods employed in the included studies were heterogeneous. The subjects included in the studies also differed in basic characteristics such as age, duration of disease and duration of follow-up. Because of these differences, despite the present analysis more randomized controlled trials are needed to verify the findings regarding the efficacy of laser treatment for onychomycosis.

5. Conclusion

Laser treatment (using a 1064-nm Nd: YAG laser or perforated CO₂ laser) for the treatment of onychomycosis has a high mycological cure rate and high safety record, and can be used successfully for the treatment and cure of onychomycosis.

Author contributions

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