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REVIEW ARTICLE

Efficacy of laser treatment for onychomycotic nails: a systematic review and meta-analysis of prospective clinical trials

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Abstract

Laser therapy for onychomycosis is emerging but its efficacy remains unestablished. To examine current evidence on efficacy of laser treatment of onychomycosis. A systematic review and one-arm meta-analysis, including all prospective clinical trials, identified on PubMed, Cochrane Library, and EMBASE databases. Trials with participants as unit of analysis (UOA), $n = 13$, were analyzed separately from trials with nails as UOA, $n = 7$. Summary proportions and 95% confidence intervals (95% CI) were calculated. Outcomes were mycological cure, clinical improvement, or complete cure. Twenty-two prospective trials (four randomized controlled trials and 18 uncontrolled trials) with a total of 755 participants were analyzed. Summary proportions with 95% CI for participants as UOA were mycological cure 70.4%, 95% CI 52.2–83.8%; clinical improvement 67.2%, 95% CI 43.2–84.7%; and complete cure 7.2%, 95% CI 1.9–23.5%. High statistical heterogeneity was detected (mycological cure $I^2 = 88\%$, $P < 0.01$; clinical improvement $I^2 = 69\%$, $P < 0.01$; complete cure $I^2 = 60\%$, $P = 0.11$). The current level of evidence is limited and with high heterogeneity, making it difficult to assess the true efficacy of laser treatment for onychomycosis. Larger randomized controlled trials with well-defined methodology are warranted.

Keywords Onychology · Laser · Mycology · Systematic review · Meta-analysis · Evidence-based medicine

Introduction

Onychomycosis (OM), a fungal infection of the nail, has an estimated global prevalence of 5.5% [1]. The disease can affect quality of life [2] by causing discomfort and social limitations, and even lead to pain and secondary bacterial infections, such as erysipelas, in high-risk patient populations afflicted with diabetes, impaired kidney function, or immunosuppression [3, 4].

The recommended treatment regimen for OM involves topical (level III evidence) and oral treatment regimens (level IA evidence), or a combination of both (level III evidence), depending on clinical presentation and severity [5, 6]. However, topical agents show limited nail permeation [7], while oral treatment is associated with systemic side effects [8]. Spontaneous remission in the absence of treatment has not been reported, meanwhile cure rates for combination treatment are ranging from 59.2 to 88.2% [9, 10], with recurrence rates of 10–53% after apparently successful treatment [6, 11].

Given the above listed difficulties, there is a need for exploring new forms of treatment for OM, hereof targeting fungal nail infections with laser devices. Numerous clinical trials aimed at investigating the efficacy of different types and settings of lasers for mycological cure and clinical clearance of onychomycotic nails [12–18]. Most of the trials conducted employ 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers with varying pulse durations for monotherapy, while more recent trials explored fractional carbon-dioxide (CO_2) lasers in combination with topical treatment [19–21]. Currently, United States Food and Drug Administration (FDA) has approved

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laser devices for *a temporary increase of clear nail* in patients with OM [22]. FDA-approved laser devices have been summarized by Nenoff et al. [23].

To date, a meta-analysis summarizing the efficacy of laser treatment for OM has not been conducted. The objective was to examine the current level of evidence and efficacy of treating OM with lasers. For this purpose, we systematically reviewed existing literature and conducted a one-arm meta-analysis of controlled and uncontrolled prospective clinical trials.

Methods

The systematic review and the meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered on the Prospective International Register for Systematic Reviews (CRD42018097329).

Literature search

The literature search was performed on online databases PubMed, Cochrane Library, and Embase, May 22, 2018. The following search terms were used: Laser; laser therapy; laser surgery; phototherapy; photothermal; nonthermal; thermal; onychomycosis; nail fungus; tinea unguium. Only English literature was included. Search strategies are shown in Supplemental Table 1. Additional studies were identified by inspecting reference lists of relevant articles. Two review authors (K.Y. and V.K.O.) assessed and screened articles for eligibility by title and abstract, followed by full-text review.

Eligibility criteria

Trials were included if they fulfilled the following criteria: (a) controlled and uncontrolled prospective clinical trials, examining the effects of laser treatment for onychomycotic nails; (b) laboratory verified mycological diagnosis at baseline; and (c) laser monotherapy for OM.

Exclusion criteria were (a) retrospective clinical trials; (b) lack of laboratory verified mycological diagnosis at baseline; (c) unclear time of follow-up; (d) participant sample size less than 10 individuals; (e) reported proportions of treated participants/nails showing 100% or 0% cure/improvement; and (f) adjuvant topical or oral antifungal treatment.

Participants were OM patients of any medical history, ethnicity, age, and gender; all clinical types, fungal types, and anatomical locations of OM were included. Treatment interventions were inclusive of all laser types, settings, and regimens.

At least one of the following outcomes had to be reported: mycological cure, clinical improvement, and/or complete cure.

Outcome definitions

Outcomes were *mycological cure*, *clinical improvement*, *and/or complete cure.* For all three outcome measures, we followed the definitions as given by the authors of the included trials and as summarized in the following:

Mycological cure was defined as at least one negative mycological laboratory test such as, but not limited to, microscopy or culture (Table 2). *Clinical improvement* was any visual nail improvement assessed by investigator at clinical examination. *Complete cure* was clinically normal nail with negative mycological examination. When trials used the terms "clinical cure" (clinically normal nail with positive or no mycological assessment) or "partial clearance," they were categorized as *clinical improvement* in this study.

Data extraction

Trial selection and data extraction were carried out by one review author (K.Y.) and verified by a second (V.K.O.). Any disagreements were resolved by discussion. The following information was extracted from each article: (1) study characteristics (study design and unit of analysis (UOA)); (2) participant characteristics (mean age and gender); (3) clinical diagnosis (OM location, duration, and clinical type); (4) mycological diagnosis (fungal strain and laboratory methods for initial confirmation and final assessment of OM); (5) laser treatment characteristics (laser type, wavelength, fluence, pulse duration, spot size, treatment passes, total sessions, and follow-up time); and (6) outcome data (clinical improvement, mycological and complete cure). Regarding the randomized controlled trials (RCTs), data for intervention-groups were extracted and included in our analyses.

Evaluation of study quality

The quality of trials was independently assessed by two reviewers (K.Y. and V.K.O.) using a quality assessment checklist by Moga et al. [24]. This appraisal tool was developed by a group of researchers at the Institute of Health Economics (IHE) in an international collaboration with researchers from two other health technology assessment (HTA) agencies in Australia and Spain using a modified Delphi technique. It consists of a checklist with 18 equally weighted criteria, including study objective, population, intervention, co-intervention, outcome measure, and statistical analysis. The maximum score is 18 "yes" responses, fulfilling 14 or more ($\geq 70\%$) as being considered of acceptable study quality.

Disagreements were resolved by consensus and referral with a third reviewer (M.H.).

Data analysis

One-arm meta-analyses were conducted using the DerSimonian-Laird random effects method to address the range of treatment parameters which required an initial logit (log (p/ (1-p)) transformation of data prior to pooled analysis. This data transformation step is statistically limited to studies reporting percentages between 0 and 100%. Due to this method-inherent limitation, studies reporting outcomes of either 0% or 100% had to be excluded. Summary proportions were calculated and reported with 95% confidence intervals (95% CI) of participants with mycological cure, clinical improvement, and/or complete cure.

Statistical heterogeneity was quantified by the I2-statistic proposed by Higgins et al. [25], and an I2-value below 25% was considered low and above 75% as high. Based on Cochrane recommendations on data visualization, funnel plots for systematic heterogeneity detection were created exclusively for outcome measures which had been reported on by a minimum of ten studies [26]. All statistical analyses were performed in the statistics program R studio (version 1.1.447) utilizing the R statistical language (version 3.5.0) and in-program software packages *metafor* and *meta*.

Results

Search results

Literature search resulted in 436 citations, hereof 208 duplicates. An additional three articles were identified [27–29] from references lists. Adjusting for duplicates, 231 articles were screened by title and abstract. After the initial screening, 191 articles were excluded, and 40 full-text articles were assessed for eligibility, with 18 not fulfilling eligibility criteria (Fig. 1).

Study characteristics

A total of 22 clinical trials from 2010 to 2018 were included, two studies having participant subgroups [15, 30], and thus, a total of 24 participant groups with 755 participants were analyzed.

Thirteen trials used participants as UOA, seven used nails, and two used both participants and nails as UOA [15, 29]. *Mycological cure* was reported in 15 trials with 16 participant groups, *clinical improvement* in 14 trials (16 participant groups), and *complete cure* in five trials (five participant groups) (Table 1).

Characteristics of involved participants and corresponding mycological diagnosis are summarized in Table 2, with only seven trials using direct microscopy and culture at final mycological examination. Two trials looked at non-dermatophyte infections [40, 41], but most trials had dermatophytes as the most frequently culture-proven fungal species at baseline. The most frequent clinical type was distolateral subungual onychomycosis (DLSO). Several trials chose to exclude all OM types (total dystrophic (TDO), proximal subungual and white superficial OM) other than DLSO [14, 30, 33, 40].

All trials except two applied 1064 nm Nd:YAG lasers to treat OM [12, 36]. Fluences ranged from 5 to 424 J/cm^2, pulse durations lasted from 0.3 to 40 ms, and target temperatures reached from 39 to 60 °C. A total of two to eight sessions were conducted, with two to five laser passes per session (Table 3).

Methodological quality of studies

Four trials were RCTs [12, 13, 34, 35], while the remaining were uncontrolled, prospective trials.

Quality of trials was assessed, resulting in eight trials achieving a score of ≥ 12 and one trial a score of 14 out of a maximum score of 18. See Supplemental Table II.

Summary proportions for trials using participants as unit of analysis

Mycological cure was reported in 12 trials with 13 participant groups. Pooled analysis showed a summary proportion of 70.4%, 95% CI 52.2–83.8%. Significant high heterogeneity was detected ($I^2 = 87\%$, $\chi^2 = 90$, df = 12, $P < 0.01$) (Fig. 2).

Clinical improvement was reported in seven trials, of which two were omitted from analysis due to reporting 100% improvement [34], and lack of raw data [18]. Therefore, five trials with five participant groups were analyzed. Analysis showed a summary proportion of 67.2%, 95% CI 43.2–84.7%. Significant heterogeneity was detected ($I^2 = 69\%$, $\chi^2 = 13$, df = 4, $P = 0.01$).

Complete cure was reported in three trials with three participant groups. One trial was left out from analysis due to reporting 0% *complete cure* [40]. Analysis showed a summary proportion of 7.2%, 95%CI 1.9–23.5%. Heterogeneity was detected ($I^2 = 60\%$, $\chi^2 = 3$, df = 1, $P = 0.11$).

Summary proportions for trials using nails as unit of analysis

Mycological cure was reported in three trials with three participant groups. Pooled analysis showed a summary proportion of 22.9%, 95% CI 7.3–52.8%. Significant high heterogeneity was detected ($I^2 = 88\%$, $\chi^2 = 16$, df = 2, $P < 0.01$).

Clinical improvement was reported in seven trials with nine participant groups; two of the trials had participants divided into subgroups [15, 30]. Pooled analysis showed a summary proportion of 56.2%, 95% CI 45.8–66.1%. Significant heterogeneity was detected ($I^2 = 70\%$, $\chi^2 = 27$, df = 8, $P < 0.01$).

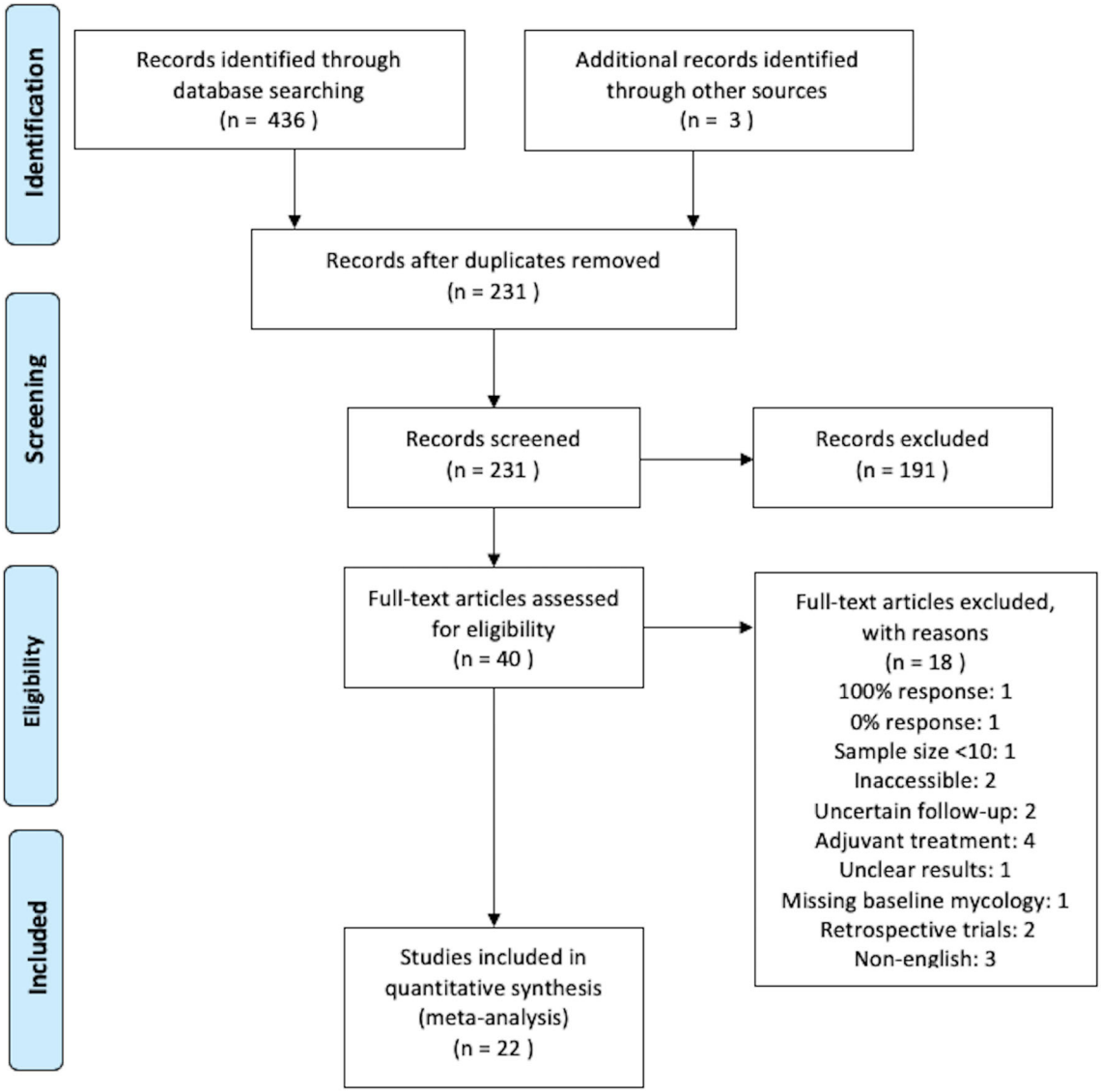

Fig. 1 Flow diagram of studies included in review of laser treatment for onychomycosis

Complete cure was reported in two trials with two participant groups. Summary proportion was 24.5%, 95% CI 3.0–77.0%. Significant high heterogeneity was detected ($I^2 = 95\%$, $\chi^2 = 21$, df = 1, $P < 0.01$) (Fig. 3).

Study heterogeneity

A funnel plot was created by plotting the logit transformed summary proportions (effect size) against the standard error of treatment effect to assess the heterogeneity detected between trials. Only one outcome measure mycological cure in participants as UOA had been reported on sufficiently to allow for visual assessment of study heterogeneity, resulting in a funnel plot with 13 data points. For easy interpretation, a summary proportion of 0.5 would equal 0 on the horizontal scale and −1.1 or 1.1 would equal 0.25 or 0.75, respectively. The funnel plot shows poor correlation between effect size and standard error of treatment effect, since a considerable number of statistical outliers is present, indicating inconsistencies in methodology among trials. Generally, trials proving little effect of treatment may be underreported in the English literature for *mycological cure* (Fig. 4).

Subgroup analysis

Subgroup analysis was performed for the most frequently reported outcome measure, mycological cure in participants as UOA.

Subgroup analysis of laser fluence and total number of sessions showed a trend towards higher cure rates for fluences ≤ 50 J/cm^2 and for total number of treatment sessions > 4; however, our findings were not statistically significant (Figs. 5 and 6).

Table 1 Characteristics and summary of reported outcome measures of studies included in the meta-analysis on efficacy of laser treatment for onychomycosis

Author	Study design	Unit of analysis	No. of participants	Follow-up (months)	Mycological cure	Clinical improvement	Complete cure	Laser system device
Kozarev 2010 [27]	Non-controlled	Participants	72	3	✓	–	–	1064 nm Nd:YAG (Fotona SP Dualis)
Landsman 2010 [12]	RCT	Nails	25	4	–	✓	–	870/930 nm diode (Nomir Noveon NaiLaser)
Kimura 2012 [31]	Non-controlled	Nails	13	4	–	✓	✓	Sub-millisecond 1064 nm Nd:YAG
Zhang 2012 [15]	Non-controlled	Participants and nails	33	6	✓	✓	–	1064 nm Nd:YAG (Pinpointe Footlaser)
Kalokasidis 2013 [32]	Non-controlled	Participants	131	1	✓	–	–	1064/532 nm Nd:YAG (Light Age Q-clear)
Noguchi 2013 [33]	Non-controlled	Participants	12	6	–	✓	–	1064 nm Nd:YAG (Candela GentleYAG)
Carney 2013[14]	Non-controlled	Nails	10	6	✓	✓	–	Sub-millisecond 1064 nm Nd:YAG
Kolodchenko 2013 [28]	Non-controlled	Participants	108	3	✓	–	–	1064 nm Nd:YAG (Fotona SP Dynamis)
Heck 2013 [29]	Non-controlled	Participants and nails	12	3	✓	✓	–	1064 nm Nd:YAG (Industra Ethera)
Hees 2014 [18]	Non-controlled	Participants	10	9	✓	✓	–	1064 nm Nd:YAG (Cynosure Elite)
Hollmig 2014 [13]	RCT	Participants	12	3	✓	–	–	1064 nm Nd:YAG (Sciton ClearSense)
Moon 2014 [16]	Non-controlled	Participants	13	1	✓	✓	✓	1064 nm Nd:YAG (Sciton ClearSense)
El-Tatawy 2015 [34]	RCT	Participants	20	6	✓	✓	–	1064 nm Nd:YAG (Fotona SP Dualis)
Wanitpha[…] 2015 [17]	Non-controlled	Nails	35	1	✓	–	–	1064 nm Nd:YAG (Fotona SP Dualis)
Kim, TI 2016 [35]	RCT	Nails	19	3	–	✓	✓	1064 nm Nd:YAG (Pinpointe Footlaser)
Kim, MS 2016 [30]	Non-controlled	Nails	13	6	–	✓	–	1064 nm Nd:YAG (FineMEC AILEEN)
Espírito-S[…] 2017 [36]	Non-controlled	Nails	30	3	✓	–	–	1064 nm Nd:YAG (Industra Ethera)
Okan 2017 [37]	Non-controlled	Participants	15	1■ and 6*	✓	✓	–	Long-pulsed 1064 nm Nd:YAG
Zalacain 2017 [38]	Non-controlled	Participants	119	3	–	–	✓	1064 nm Nd:YAG (Intermedic S30 Podylas)
Piccolo 2017 [39]	Non-controlled	Participants	20	2	–	✓	–	1064 nm Nd:YAG (DEKA)
Leverone 2018 [40]	Non-controlled	Participants	17	12	✓	✓	✓	1064 nm Nd:YAG (Cutera Genesis)
Ibrahim 2018 [41]	Non-controlled	Participants	16	9	✓	–	–	1064 nm Nd:YAG laser (Cynosure Elite)

RCT, randomized controlled trial; *UOA*, unit of analysis

■ Follow-up time for mycological cure assessment. *Follow-up time for clinical improvement assessment

Table 2 Characteristics of involved participant groups in studies included

Author	Mean age (years)	Male (%)	Mean OM duration (years)	OM location	DLSO type (%)	TDO and PSO type (%)	Severity at baseline♣ (%)	Initial mycological examination	Final mycological examination	Dermatophyte at baseline (%)
Kozarev	NA	NA	NA	Toe and finger	53	8.3 and 31	NA	Culture	Culture	81.9
Landsman	NA	NA	NA	Toe	62	0 and 0	34	Culture and PAS	PAS	88.4
Kimura	67.8	30.7	7.8	Toe	69	23 & 7.7	70	KOH	KOH	NA
Zhang Group 1	50.3	40	16.4	Toe and finger	NA	NA	50* (12 ≤ SCIO < 15)	KOH	KOH	NA
Zhang Group 2	47.3	20	14.8	Toe and finger	NA	NA	42* (12 ≤ SCIO < 15)	KOH	KOH	NA
Kalokasidis	NA	28.2	NA	Toe and finger	94	9.9 and 0.8	67 (OSI: 16–30)	Culture	KOH and culture	85.4
Noguchi	53.5	50	NA	Toe	100	0 and 0	NA	PCR and culture	NA	100
Carney	58	50	NA	Toe	100	0 and 0	NA	Culture	KOH and culture	100
Kolodchenko	39.4	35	NA	Toe and finger	89	6.5 and 2.8	NA	Culture	KOH	88
Heck	58	25	3.5	Toe and finger	NA	NA	NA	KOH	KOH	NA
Hees	69.4	90	NA	Toe	NA	NA	NA	Culture	Culture	100
Hollmig	53	83	NA	Toe	NA	NA	NA	Culture	Culture	67
Moon	59.6	38	2.7	Toe and finger	92	0 and 0	NA	KOH and culture	KOH	92.3
El-Tatawy	39	0	2.3	Toe and finger	60	20 and 20	NA	KOH and culture	Culture	90
Wanitphak[…]	58.4	48.6	NA	Toe and finger	91	9.5 and 0	NA	KOH and culture	KOH and culture	50
Kim, TI	62.4	63	NA	Toe and finger	39	56 and 0	NA	KOH and culture	KOH and culture	89.4
Kim, MS Group 1	63.1	71	NA	Toe and finger	100	0 and 0	100 (OSI)	KOH and culture	KOH	100
Kim, MS Group 2	60.2	57	NA	Toe and finger	100	0 and 0	100 (OSI)	KOH and culture	KOH	100
Espírito-Santo	53.2	23.3	7.5	Toe	NA	NA	NA	KOH and culture	KOH and culture	90.3
Okan	NA	7	NA	Toe	40	29 and 36	NA	Culture	Culture	86.7
Zalacain	NA	NA	NA	Toe	62	34 and 1.7	NA	KOH and culture	Culture	79.8
Piccolo	42	20	NA	Toe	NA	NA	NA	Culture	NA	NA
Leverone	NA	NA	NA	Toe	100	0 and 0	NA	KOH and culture	KOH and culture	0♦
Ibrahim	NA	6.3	NA	Toe and finger	81.3	12.5 and 0	NA	KOH and culture	KOH and culture	0

OM, onychomycosis; *DLSO*, distal and lateral subungual onychomycosis, *OSI*, onychomycosis severity index; *SCIO*, the scoring clinical index for onychomycosis; *KOH*, potassium hydroxide; *PCR*, polymerase chain reaction; *PAS*, periodic acid-Schiff stain; *NA*, not available; *TDO*, total dystrophic onychomycosis; *PSO*, proximal subungual onychomycosis

*Reported as proportion of nails. ♣Proportion of nails or participants rated severe by clinical investigator. ♦100% of nails infected with Neoscytalidium dimidiatum fungal strain

Table 3 Summary of laser treatment settings

Author	Fluence (J/cm^2)	Pulse duration (msec)	Frequency (Hz)	Spot size (mm)	Temperature (°C)	Passes	Total sessions	Weeks between sessions	Nail debridement pre-treatment	Topical agent between digits
Kozarev	35 to 40	35	1	4	50	3	4	1	Yes	No
Landsman	424 and 204	NA	NA	15	< 39	2	4	Varying	Yes	Yes
Kimura	14	0.3	5	5	NA	2	2.5	4 and/or 8	No	No
Zhang Group 1	240 to 324	30	1	3	NA	3	8	1	No	No
Zhang Group 2	240 to 324	30	1	3	NA	3	4	1	No	No
Kalokasidis	14	NA	5	2.5	NA	2*	2	4	Yes	No
Noguchi	10	0.5	2	6	NA	4	3	4	No	No
Carney	16	0.3	2	5	NA	5	2	Varying	No	No
Kolodchenko	35 to 40	35	NA	4	ca. 50	2	4	1	6 of 108 participants	No
Heck	50 to 80	40	NA	6	NA	2	3	2	No	No
Hees	50	40	NA	3	NA	4	2	4	No	Yes
Hollmig	5	0.3	6	6	40 to 42	2 to 3	2	2	No	No
Moon	5	0.3	5	6	40 to 42	NA	5	4	No	No
El-Tatawy	35 to 40	35	1	4	NA	3	4	1	No	No
Wanitphakdeedecha	35 to 45	30 to 35	1	4	NA	2	4	1	No	No
Kim, TI	NA	0.1	30	1.5	40 to 60	2	3 to 4	4	Yes	No
Kim, MS Group 1	16	0.3	10	5	NA	NA	8	1	No	No
Kim, MS Group 2	225	0.6	5	2	NA	NA	8	1	No	No
Espírito-Santo	22 to 25	5	1.5 to 2.5	6	NA	NA	NA	NA	NA	NA
Okan	40 to 60	25	NA	4	NA	2	4	1	Yes	No
Zalacain	35 to 40	NA	1	3	< 47 ± 4	3	3	2	No	No
Piccolo	30	5	1	4	NA	3	4	1	No	No
Leverone	16	0.3	3	5	40.9 to 56.5	4	4	6	No	Yes
Ibrahim	40	30	1	NA	NA	3	4	1	No	No

NA, not available

*Second pass was performed at 532 nm wavelength

Discussion

Results of this meta-analysis indicate laser treatment for OM has an effect, with the highest summary proportions reached in trials using participants as UOA for *mycological cure*, 70.4%, followed by *clinical improvement,* 67.2%, and at last *complete cure,* 7.2%. Summary proportions in trials using nails as UOA were lower for *mycological cure*, and higher for *complete cure*. However, these findings must be interpreted with caution due to the notable variation across studies. The heterogeneity detected could be due to differing participant pools and mycological diagnoses, disparity in interventions, and methodological variations in trials such as differences in exclusion criteria applied (Supplemental Table III), as well as inconsistencies in definitions of outcome, choice of analysis, and diagnostic techniques. This study did not account for these described variations. It is well-known that participant age and clinical subtype of OM influence the response to therapy [42]. With the mean age of participants ranging from 39 to 69 years and the proportion of nails/participants with DLSO and TDO ranging from 53 to 100% and 0 to 34%, different responses to therapy for some groups can be expected. In addition, up to 17 trials did not assess clinical severity and duration of OM, which may be important contributing factors to heterogeneity.

False negative tests and insufficient follow-up could be possible fallacies in many of the included trials, since 15 out of 22 trials either used direct microscopy or culture at final mycological examination, but not in combination, which consequently increases odds of false negative results. This could explain why analyses showed that trials with participants as UOA had a higher summary proportion for mycological cure compared to mycological cure in trials using nails as UOA, since all trials using nails as UOA used direct microscopy combined with culture at final

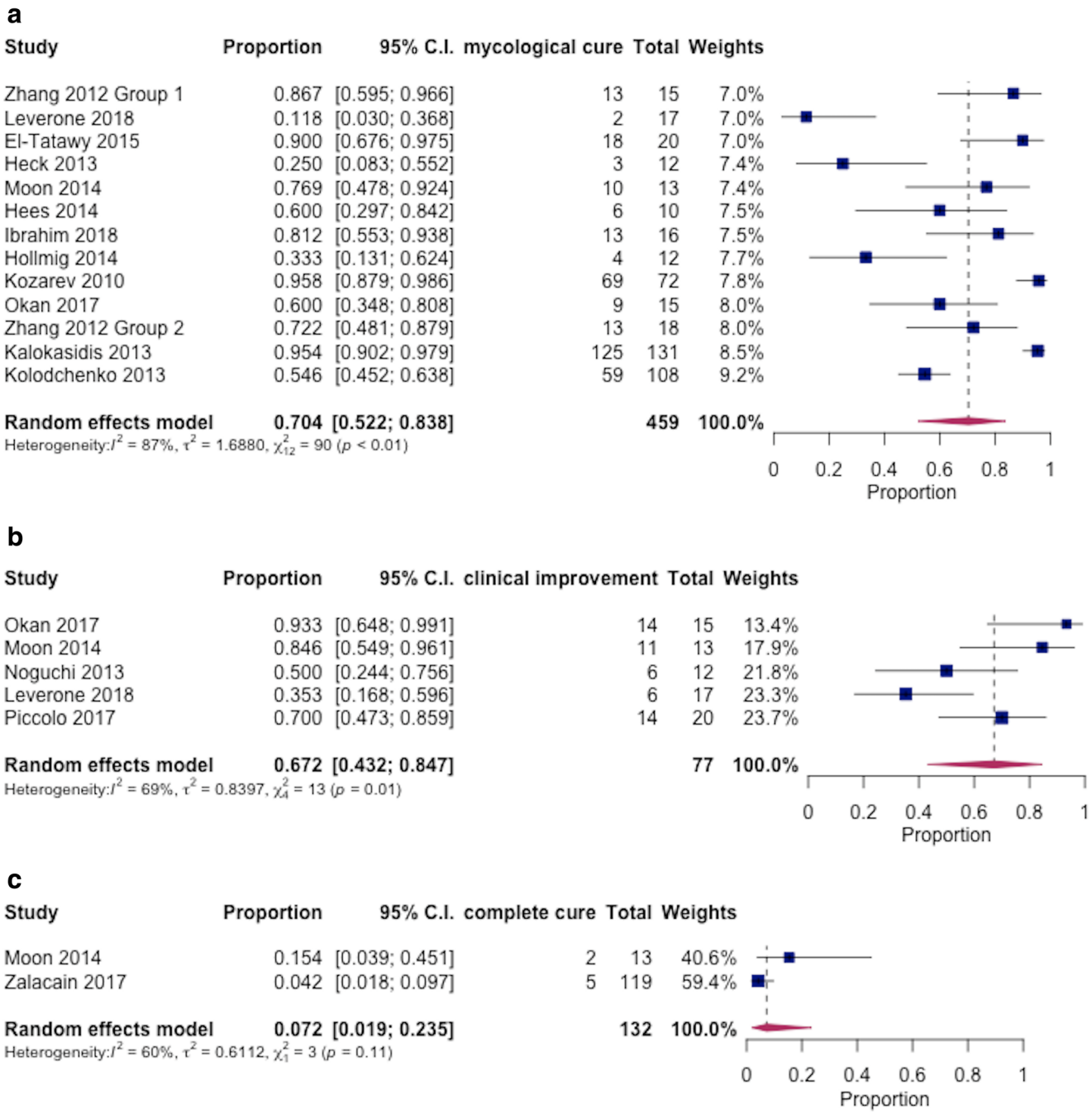

Fig. 2 Forest plot showing proportion and corresponding 95% confidence intervals of participants with (**a**) *mycological cure*, (**b**) *clinical improvement*, and (**c**) *complete cure* in studies with participants as unit of analysis. Trials sorted by weight (%)

mycological examination. Furthermore, summary proportion for *complete cure* was unexpectedly high in the analysis for trials using nails as UOA, 24.5%. One of the included trials contributed to this high summary proportion by reporting a proportion of 51% nails being completely cured [31], which could be caused by the investigator's sole use of direct microscopy at final mycological assessment.

Duration of follow-up in trials ranged between 1 and 12 months with a mean duration of 4 months and thereby shorter than current FDA recommendations of 6 months for fingernails and 12 months for toenails [22]. Many trails did not stratify fingernails and toenails, and only one trial met the FDA recommendations of follow-up for toes [40].

In literature, multiple studies reviewed the efficacy of lasers for OM, but only one was performed systematically [43]. The findings of previous reviews are in accordance with results of this meta-analysis, all of which conclude difficulties comparing results across trials due to inconsistencies and limited

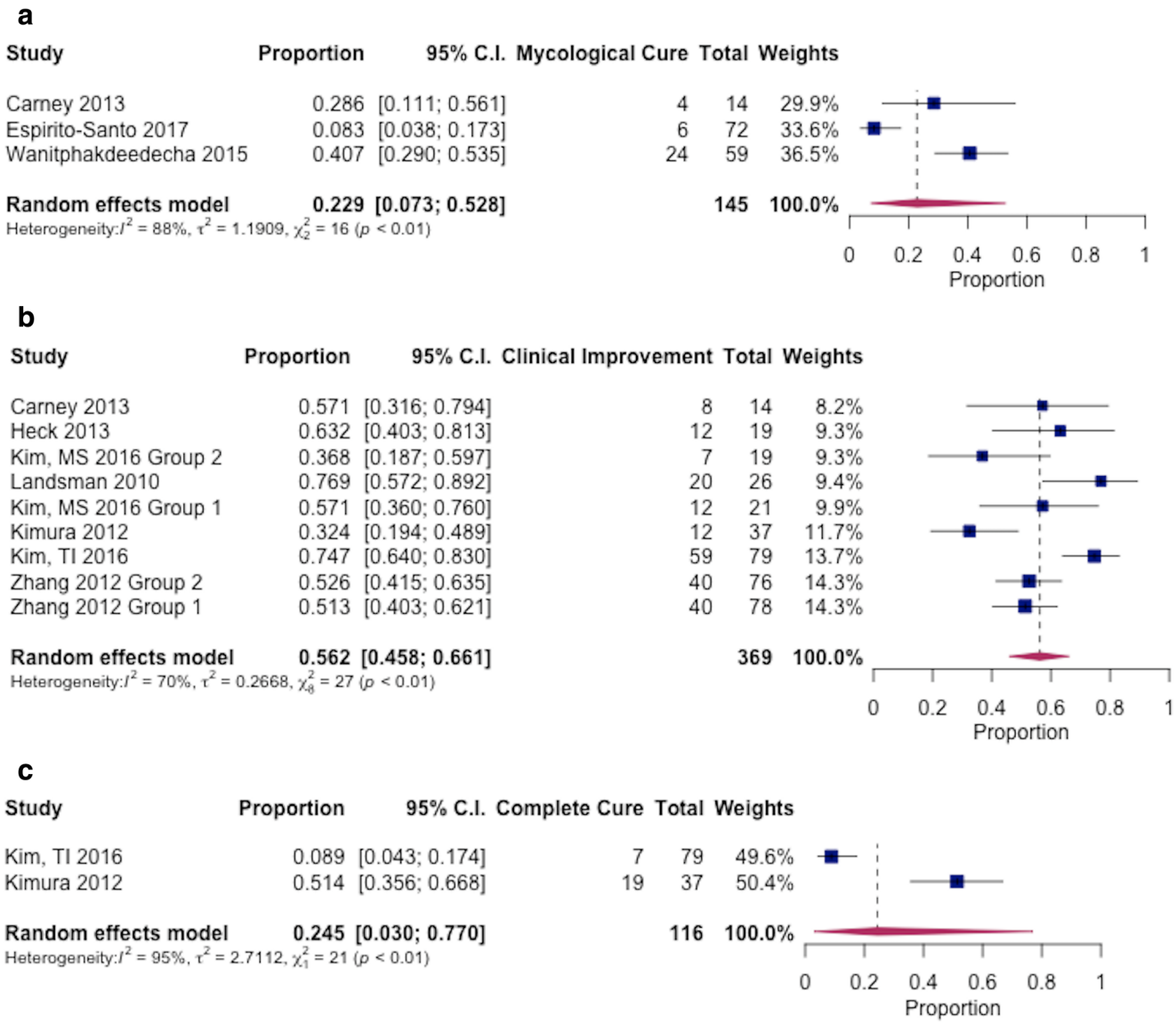

Fig. 3 Forest plot showing proportion and corresponding 95% confidence intervals of nails with (**a**) *clinical improvement* and (**b**) *complete cure* in trials with nails as unit of analysis. Trials sorted by weight (%)

amount of high-quality evidence [43–49]. One clinical review has undertaken a quantitative analysis and calculated higher cure rates for clinical improvement than mycological cure [45] for participants as UOA. However, the analysis was limited by applying equally weighted averages across trials. Results of the subgroup analyses were not statistically significant but suggestive of the impact laser fluence, and number of treatment sessions could have on mycological cure rates. These findings are in agreement with a previous study published in 2018 [50], which stated the optimal fluence for long-pulsed 1064-nm Nd:YAG laser treatment for onychomycosis caused by trichophyton rubrum to be 45 J/cm2, and number of treatment sessions to be six.

Limitations of this study were the quantity of uncontrolled trials compared to RCTs. Four RCTs have been published but were unfit for comparison due to inconsistencies in UOA and control-interventions for comparator-groups. Two RCTs applied sham-interventions for comparator-groups while their UOA differed [12, 13]. The remaining RCTs applied topical antifungal treatment for comparator-groups [34, 35], but UOA differed. The intervention-groups from RCTs were extracted and analyzed as uncontrolled trials in this study, and for the sake of simplicity, quality of these RCTs was evaluated with the same appraisal tool as for uncontrolled trials. With the given evidence, a systematic review and a meta-analysis of uncontrolled clinical trials were performed with the addition of intervention-groups from RCTs, omitting the data for comparator-groups.

Furthermore, data analysis was limited by trials with participants as UOA failing to report the number of nails being

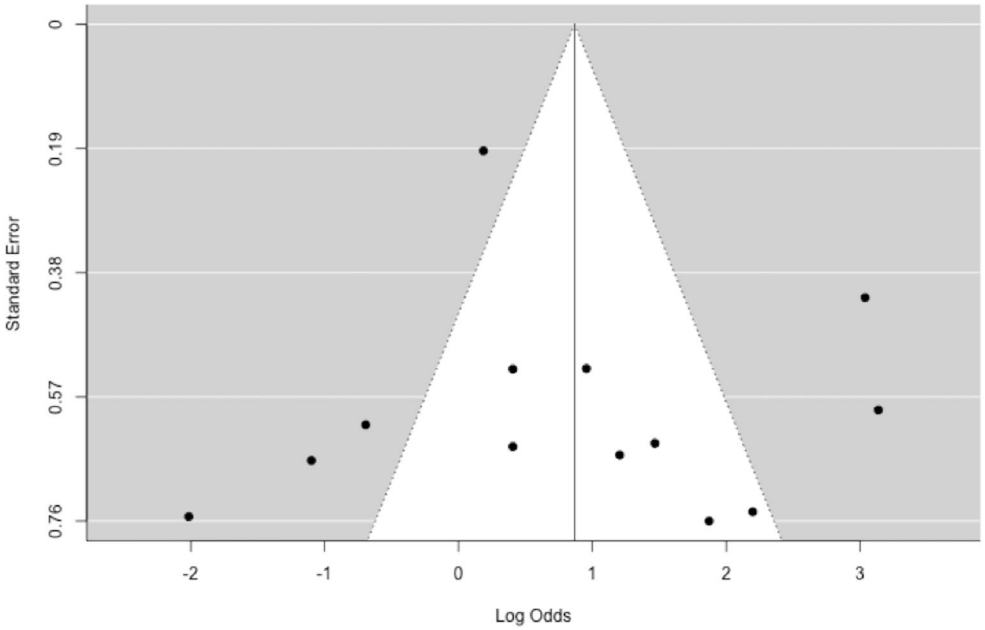

Fig. 4 Funnel plot of trials reporting *mycological cure* in participants as UOA

analyzed per participant; only five trials reported the number of nails being analyzed per participant [14, 18, 31, 33, 40]. This would lead to biased cure and/or improvement proportions depending on the number of nails analyzed per participant. Another concern was trials with nails as UOA having participants contribute more than one nail for analysis (repeated measures), which may result in too small a standard error of estimated summary proportions.

This meta-analysis supports FDA's clearance of laser devices for a temporary increase in the amount of clear nail in patients with OM, but the current body of evidence is too sparse and inconsistent to draw firm conclusions on efficacy

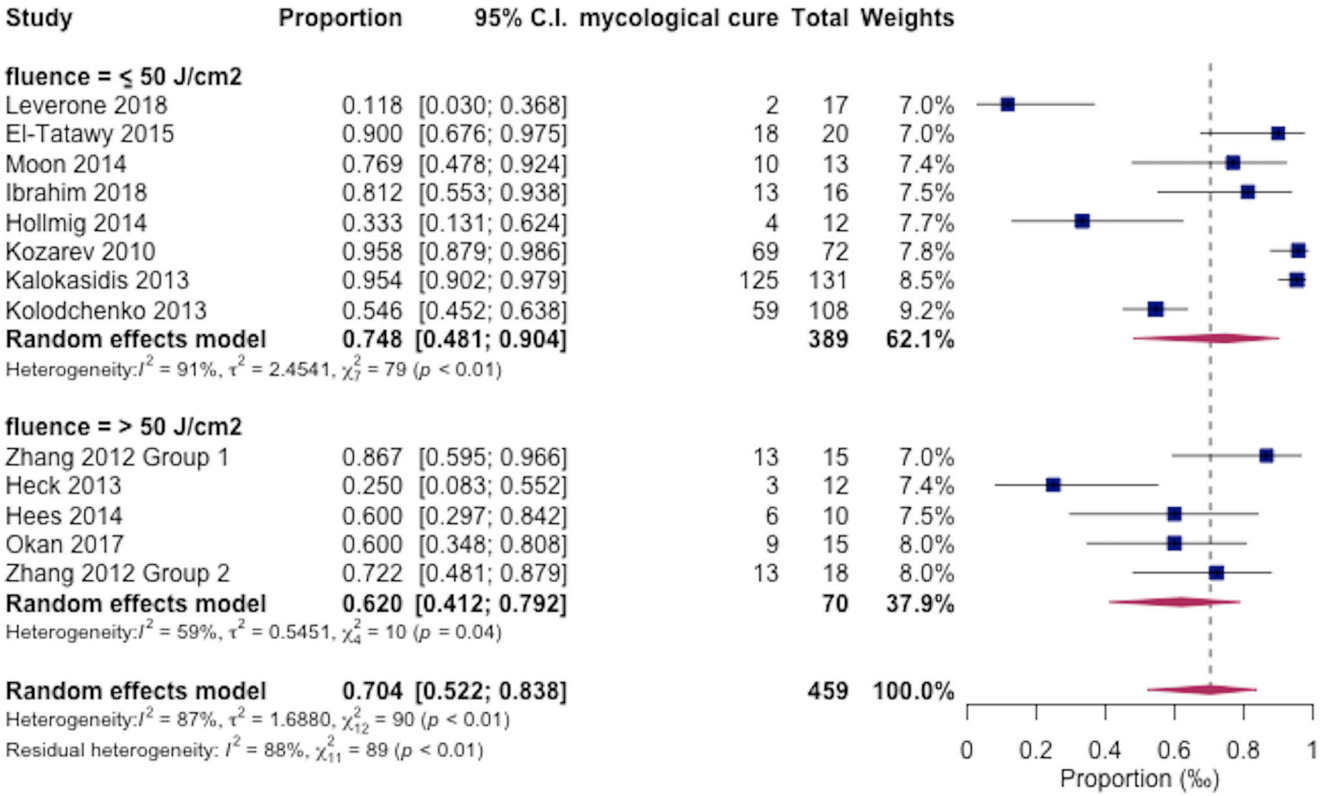

Fig. 5 Subgroup analysis of trials using laser fluences over or under 50 J/cm^2

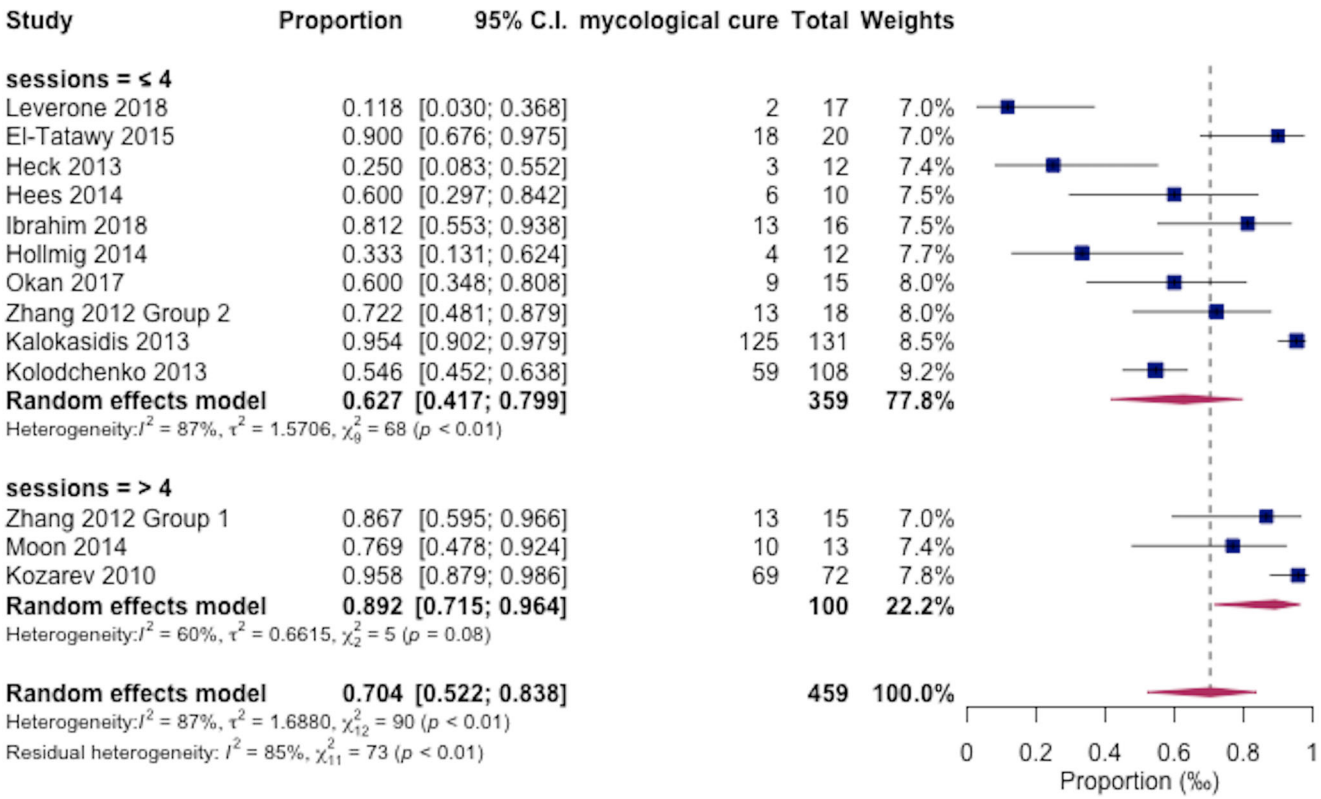

Fig. 6 Subgroup analysis of trials based on total number of treatment sessions

of laser treatment for mycological cure [22]. There is a growing need for low-risk treatment options with no systemic adverse events and drug interactions in high-risk patient populations with onychomycosis [51]. Lasers should be a possible treatment option to have in mind, especially given the rising OM prevalence among a steadily increasing elderly patient population [52]. More RCTs in this field of research could help corroborate the efficacy of laser treatment of onychomycosis.

Conclusion

We calculated summary proportions for mycological cure, clinical improvement, and complete cure in participants with onychomycosis treated with laser. The currently available literature comprises primarily uncontrolled trials showing significant study heterogeneity making it difficult to summarize and assess the efficacy of laser treatment for onychomycosis.

Given the limited evidence for laser treatment of onychomycosis, large-scale randomized, controlled clinical trials with consistent comparator-groups, treatment settings, and well-defined methodology including clear outcome definitions are warranted.

Compliance with ethical standards

Conflict of interest VK Ortner has received research grants from LeoPharma and InnovationFund Denmark. M Haedersdal has received research grants from Sebacia Inc., Procter & Gamble, Lutronic, LeoPharma and Galderma.

Abbreviations DLSO, distolateral subungual onychomycosis; FDA, Food and Drug Administration; Nd:YAG, neodymium-doped: yttrium-aluminum-garnet; Nd:YAP, neodymium-doped: yttrium-aluminum-perovskite; OM, onychomycosis; RCT, randomized controlled trial; TDO, total dystrophic onychomycosis; UOA, unit of analysis

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