To evaluate the efficacy and safety of laser interventions for facial acne scars: a systematic review and Bayesian network meta-analysis

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Background: There are numerous laser treatments for acne scars in clinical practice. However, there are no clinical studies comparing all laser methods to provide an evidence-based bias for clinicians to choose the best strategy. Therefore, this systematic review and network meta-analysis was conducted to explore the efficacy of different types of laser treatment on acne scars. This study can provide the most effective treatment for acne scars in clinical practice.

Methods: The databases of PubMed, Embase, Cochrane Library, and Web of Science were searched from their inception to July 2022. The Cochrane risk of bias assessment tool was used to assess the bias of the included original studies. Bayesian network meta-analysis was used to investigate the efficacy of laser treatment strategies in scar improvement, cure rate, and satisfaction.

Results: As shown by the results, the top 3 treatment options for scar improvement were fractional carbon dioxide laser (FCL) + platelet-rich-plasma (PRP) [surface under the cumulative ranking curve (SUCRA): 0.699], 1064Nd (1,064-nm neodymium-doped yttrium aluminum garnet picosecond laser) + 15%VC (Vitamin C; SUCRA: 0.675), and 1064Nd (SUCRA: 0.627). The standard mean difference (SMD) of FCL + PRP was −1.76 (95% CI: −3.49, −0.03), compared with that of FCL. The top 3 treatment options for improving cure rate were Er (Er:YAG laser treatment) + PRP (SUCRA: 0.873), FCL (SUCRA: 0.773), and FCL + 30% salicylic acid (30%SC) (SUCRA: 0.772). The RR of Er + PRP cure rate was 13.86 (95% CI: 1.79, 107.22), compared with non-laser radiofrequency therapy.

Conclusions: The findings suggested that combined therapies should be used to treat acne scars. Er + PRP showed the highest cure rate of acne scar, followed by FCL + 30%SC or FCL monotherapy. FCL combined with PRP could improve acne scarring to the greatest extent, and 1064Nd combined with 15%VC can also exert a good effect. As for satisfaction, FCL monotherapy was the most satisfactory methods for patients, followed by PRP monotherapy. Therefore, Er + PRP and FCL + PRP can be used as the first choice for clinical treatment of acne scars. Additionally, using FCL alone is also an effective and elective treatment method due to its affordable cost and comfort.

Keywords: Laser; acne scar; network meta-analysis

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Introduction

Acne vulgaris, a chronic inflammatory disorder confined to pilosebaceous units, is characterized by pimples, papules, pustules, and nodules, and is often complicated with scars (1). The onset of acne usually occurs in puberty, affecting approximately 27% of adolescents and 93% of late teens. The face, neck, chest, and upper back are the regions typically affected by acne vulgaris (2). The etiology is complicated, including increased sebum secretion induced by androgens, inflammatory keratinization, colonization of *Cutibacterium acnes* in the pilosebaceous unit, delayed immune response, diet, and genetic factors (3). Different skin lesions may occur at different stages of the formation and remission of acne vulgaris. Acne scarring is now a common disease leading to impaired facial appearance and significant negative effects on patients' mental health and daily life (4). Among the population aged 11–30 years, 80% may experience acne at some point, with subsequent scarring affecting about 40% (5). Among the types of scars, the depressed acne scar is relatively serious, which manifests the likeness of an orange peel, ice pick, meteorite crater, and so on (6). Acne scarring is associated with people's satisfaction with their appearance, low self-esteem, and inferiority complex, which can result in anxiety, depression, and even suicidal thoughts (7).

With the increasing demand for beauty, the healing of acne scars is the focus and challenge of acne treatment.

Highlight box

Key findings

- This study has identified a meaningful therapeutic approach for acne scars.

What is known and what is new?

- A large number of existing randomized controlled experiments have compared 2–3 acne scar treatments, or a single method for meta-analysis.
- To date, there has been no research on the use of network meta-analysis to compare all laser treatments. This study evaluates the efficacy and safety of laser interventions in the treatment of acne scars, which is an innovative point.

What is the implication, and what should change now?

- This research is more comprehensive, involving more types of lasers, and the results are more instructive. In the future, based on the results of this trial, we should conduct further clinical trials of the most effective treatment to prove the significance of this treatment for acne scars.

Currently, acne scars are treated with grinding, surgical release, plasma therapy, autologous fibroblasts, platelet-rich-plasma (PRP), and laser therapy, among others. Different treatments for acne scars have different effects and complications (8). At present, laser treatment is the most common method for treating acne scars. The principle of laser treatment is photothermy. Relevant studies have demonstrated that different laser parameters and techniques might have different efficacy on different forms of acne scars (9). The commonly used laser treatments include the 1,064 nm long pulsed neodymium: yttrium-aluminum-garnet (Nd:YAG) laser (1064Nd), 1,550 nm Erbium: glass fractional laser (1550Er), fractional CO_2 laser (FCL), 2,940 nm erbium fractional laser (2940FEL), picosecond 755 nm alexandrite laser (755PAL), pulsed dye laser (PDL), and so on. Currently, there are various types of laser treatments for acne scars, but the pros and cons of different laser intervention methods in scar treatment still remain controversial.

The main role of network analysis is to comprehensively evaluate and rank all the interventions in the same body of evidence simultaneously. It can combine both direct and indirect comparisons, which cannot be accomplished by conventional meta-analysis. Therefore, this Bayesian network analysis was conducted to investigate the effect of diversified laser treatment methods on acne scar with the aim of providing a reference for clinical practice. Through searching, we found that there were conflicting results between some studies on the treatment of acne scars. Up to now, there is still a lack of network meta-analysis basis for the selection of laser. Therefore, we carried out this research analysis to explore the optimal method for acne scars. We present the following article in accordance with the PRISMA-NMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5997/rc).

Methods

This systematic review was registered on PROSPERO (ID: CRD42022361585).

Retrieval strategy

Based on the Cochrane Collaboration criteria, the databases of PubMed, Web of Science, Embase, and Cochrane were searched for publicly published randomized controlled trials

(RCTs) on laser treatment or combined therapy of laser treatment and other non-laser treatment for acne scars. We also screened relevant meta-analyses published previously. Subject terms and free words were used in the retrieval process, and there was no restriction on region or language. The subject terms mainly included acne, acne vulgaris, and laser, or their synonyms. The detailed retrieval strategy is presented in Table S1.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

- Population: Patients diagnosed with pathological acne scarring.
- Intervention: Treatment including laser (monotherapy or combined therapy).
- Comparison: Different types of lasers, medication, or other non-laser therapeutic strategies.
- Outcome: ECCA score (échelle d'évaluation clinique des cicatrices d'acné), GBS score (Goodman & Baron quantitative global scarring grading system), cure rate (blinded dermatologists using a quartile grading scale for assessment of clinical improvement of skin smoothness: Grade 1: 0–25% = poor improvement, Grade 2: 26–50% = fair improvement, Grade 3: 51–75% = good improvement, and Grade 4: >75% = excellent improvement), satisfaction (on the last visit, the patients were asked to rate the appearance of the scar, skin texture, and overall satisfaction compared with these factors before treatment on a scale of 1: not satisfied, 2: slightly satisfied, 3: satisfied, and 4: very satisfied).
- Study design: The included original studies were RCTs.

The exclusion criteria were as follows:

- Population: Patients with non-pathological acne scars.
- Intervention: Studies that did not include laser treatments, or the studies used different treatment frequencies/cycles of the same type of laser.
- Comparison: There was a lack of control groups in the study.
- Outcome: In the original study, there was a lack of outcome measures evaluating scar improvement, such as cost analyses.
- Study design: The included original studies were non-RCTs (e.g., retrospective studies, single-arm studies, reviews, etc.).

Interventions

In the included studies, the intervention group mainly used laser therapy, and other therapies combined with non-laser treatment were considered as independent interventions in our meta-analysis to reduce the bias caused by other non-laser therapies.

Literature screening and data extraction

The retrieved literature was imported into Endnote (Clarivate, London, UK). After excluding the duplicated publications, the original studies were screened by titles or abstracts to obtain initially eligible studies. The eligible studies finally included in this research were selected based on the full text. Before data extraction, a standard data extraction spreadsheet was made and the content included title, author, year, comparison, intervention, sample size, intervention protocol, acne scar evaluation form (ECCA and GBS), patients' satisfaction, response rate, complications, and so on.

The aforementioned literature screening and data extraction were conducted independently by 2 researchers (ZXZ and QL) and cross-checked after completion. If there was any dissent, a third investigator (WHC) was consulted to make a decision.

Quality assessment

Two independent researchers evaluated the risk of bias in the included studies using the Cochrane Collaboration Risk of Bias Tool. Upon the completion of the quality assessment, they cross-checked their results. Any disagreements were solved by a third researcher. The risk of bias assessment by the Cochrane tool involved 7 items in 6 domains: (I) selection bias (random sequence generation, Allocation concealment); (II) performance bias (blinding of participants and personnel); (III) detection bias (Blinding of outcome assessment); (IV) attrition bias (incomplete outcome data); (V) reporting bias (selective reporting); (VI) other bias. Each item was answered as "high risk of bias", "low risk of bias", or "unclear".

Statistical analysis

Network meta-analysis uses the Bayesian random-effects model to compare the effectiveness of various interventions. The Markov chain Monte Carlo method was used for modeling, with four Markov chains running at the same time and the number of annealing set to 20,000. After

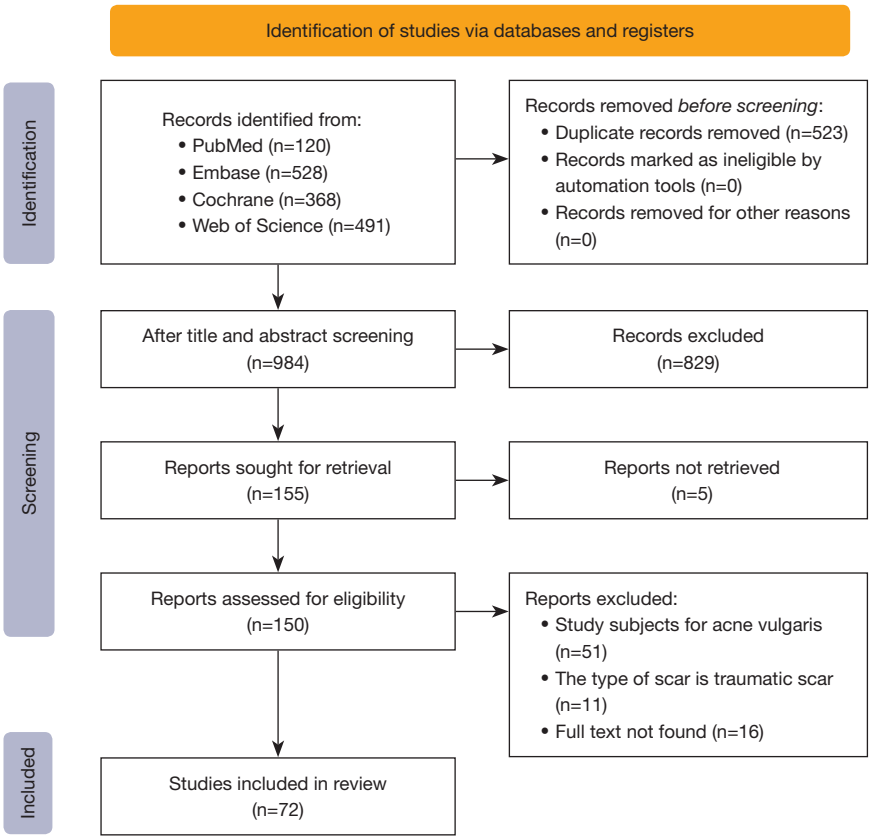

Figure 1 The flowchart of literature screening.

50,000 simulation iterations, a model was constructed. The Deviation Information Criterion (DIC) was used to analyze the model fitting and global variable consensus. If there were closed loops, we would use the node-splitting method to analyze the local consensus. Furthermore, interventions were sorted based on surface under the cumulative ranking curve (SUCRA), and a league table was generated to present the difference in the effectiveness between interventions (Table S2). A funnel plot was used to directly reflect the heterogeneity among the studies. Stata 15.0 (Stata Corporation, College Station, TX, USA) was used for data analysis. A $P<0.05$ indicates statistical significance.

Results

Literature search

After the literature search by subject terms and free words, 120 articles were found in PubMed, 528 in Embase, 368 in Cochrane, and 491 in Web of Science. After excluding 523 duplicated publications, 984 articles remained. Afterwards, 155 articles were screened by reading of titles and abstracts. Articles were excluded if the full text was not available or the research subjects did not meet the inclusion criteria. A total of 72 articles were finally included (*Figure 1*).

The basic characteristics of the included studies

After downloading the full text for screening, a table of basic characteristics was created to extract the basic characteristics of the included studies (*Table 1*). Among the 72 included articles, 18 were from Egypt, 13 from China, 11 from Korea, 8 from Thailand, 5 from the USA, 6 from India, 2 from Iraq, 1 from Indonesia, 1 from the UK, 2 from Turkey, 1 from Belgium, 1 from Brazil and 3 from Iran. The sample size was between 5 and 350 cases, and the publication time was from 2004 to 2022.

Quality evaluation

The included studies were all RCTs. There were 3 methods of random allocation among the included studies: the

Table 1 Basic information of the included literatures

No.	Author	Year	Study design	Country	Intervention	Number of cases [faces]	Total number of samples [faces]	Gender (male/female)	Age, years	Course of the disease	Course of treatment	Follow-up time	Outcome indicator
1	Zhang YJ (6)	2022	Randomized, split-face study	China	30% supramolecular salicylic acid + ultra-pulsed CO_2 fractional laser; ultra-pulsed CO_2 fractional laser	20; 20	20 [40]	–	–	–	–	3 months	ECCA
2	Wang Y (10)	2022	Randomized	China	Fractional CO_2 laser; fractional CO_2 laser + PRP + Yifu	350; 350	700	66 M 84 F; 64 M 86 F	15–31; 16–32	1–2 years	–	–	Clinical effect, ECCA, DLQI, VSS
3	Sabry HH (11)	2022	Split-face comparative double-blinded	Egypt	Long-pulsed Laser Nd:YAG 1,064 nm; fractional CO_2 laser	20; 20	20 [40]	–	At least 18	–	–	–	–
4	Lu K (12)	2022	Prospective, simultaneous spilt-face	China	Fractional non-ablative 1,927 nm thulium laser (FTL) 1,927 nm; fractional ablative 2,940 nm Er:YAG laser (FEL) 2,940 nm	27; 27	27 [54]	16 M 11 F; 16 M 11 F	26; 26	–	–	–	GBS, patients' satisfaction
5	Gawdat HI (13)	2022	Split-face randomized	Egypt	PRP 'fluid + fractional CO_2 laser; PRP 'gel + fractional CO_2 laser	27; 27	27 [54]	–	–	–	–	–	Clinical assessment scores, ECCA
6	Emam AAM (14)	2022	Split-face comparative	Egypt	2,940 nm fractional Er: YAG laser	21; 21	21 [42]	–	–	–	16 weeks	3 months	GBS
7	Allam N (15)	2022	Randomized clinical	Egypt	Monopolar radiofrequency; pulsed dye laser	15; 15	30	–	–	–	1 session (8 minutes for each cheek) per month of MFR for 4 months. 1 session (5 minutes for each cheek) per month of PDL for 4 months	–	ECCA, FASQoL (this is a 10-item assessment tool with 3 do-mains for evaluating the emotional, social, and work/school-related effect of scars), SCARS [self-assessment questionnaire (using a scale of 0–10)]
8	Sirithanabadeekul P (16)	2021	Randomized split-face comparative	Thailand,	Fractional picosecond 1,064-nm laser; fractional CO_2 laser	25; 25	25 [50]	–	–	–	3 months	–	Skin imaging, physician improvement scores
9	Shi Y (8)	2021	Randomized, split-face, double-blind	China	Fractionated frequency-doubled 1,064/532 nm picosecond Nd:YAG laser; non-ablative fractional 1,540 nm Er: glass laser	22; 22	22 [44]	–	–	–	4 monthly treatments	1 month	ECCA, PRIMOS (a 3D imaging system), two physicians (with 15 and 30 years of work experience, respectively), who were blinded to the grouping, evaluated the treatment efficacy
10	Rajput CD (17)	2021	Prospective, nonrandomized, open-label	India	Fractional CO_2 laser; fractional microneedling radio frequency	25; 25	50	–	–	–	4 sessions were given for both the groups at an interval of 2 months	–	GBS
11	Pratiwi I (18)	2021	Double-blind, randomized controlled	Indonesia	Long-pulsed Laser Nd:YAG 1,064 nm + Vitamin C; long-pulsed Laser Nd:YAG 1,064 nm	9; 9	18	–	–	–	–	–	GBS
12	Lan T (19)	2021	Pilot randomized Split-face clinical	China	Fractional micro-plasma radiofrequency; fractional microneedle	60; 60	60 [120]	39 M/21 F	17–30 (average 22.87 ±2.51)		3 applications of treatment at 2-month intervals	1, 3, 6 months after the final treatment	ECCA, dermatologists evaluation, patient self-evaluation, DLQI scores, adverse effects
13	Kimwattananukul K (20)	2021	Double-blind, placebo-controlled	Thailand	0.5% timolol maleate; normal saline; fractional CO_2 laser	25; 25	25 [50]	12 M/13 F	18–50, mean 31.4	At least 3 months	–	–	Skin hydration, crusting score
14	Feng H (21)	2021	Randomized, evaluator-blinded, left-to-right split-face	China	Intense pulsed light; fractional 1,064 nm Nd:YAG picosecond laser + intense pulsed light	15; 15	15 [30]	–	18–60	–	–	five sessions of treatment at weeks 0, 4, 8, 12, 16 and were followed up at week 28	ECCA, DLQI, TEWL, MI

Table 1 *(continued)*

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No.	Author	Year	Study design	Country	Intervention	Number of cases [faces]	Total number of samples [faces]	Gender (male/female)	Age, years	Course of the disease	Course of treatment	Follow-up time	Outcome indicator
15	El-Hawary EE (22)	2021	Comparative clinico-immuno-histopathological	Egypt	PRP; ablative fractional CO_2 laser; PRP + FCO_2	20; 20; 20	60 [22M/38F]	40% M/60% F; 40% M/60% F; 30% M/70% F	Aged 20–35 (mean 24.60±3.20)	–	Each group received 3 sessions at monthly intervals	–	Clinical, histopathological
16	Cheng X (23)	2021	Randomized split-face	China	10,600 nm ablative fractional laser; 1,565 nm nonablative fractional laser	19; 19	19 [38]	–	–	–	–	–	Erythema, crusting durations, and degree of pain
17	Chen L (24)	2021		China	2,940 Er:YAG laser treatment in the microlaser peeling; fractional ablative laser; combined modes	30; 30; 30	90	–	–	–	–	–	ECCA, self-evaluation of treatment satisfaction by the patient
18	Al-Dhalimi MA (25)	2021	Split-face clinical comparative	Iraq	2,940 nm fractional Er: YAG laser; long pulsed Nd:YAG 1,064 nm laser	20; 20	20 [40]	–	–	–	3 sessions at a 3-week interval	–	Sharquie scores, digital photographic assessment, patient's satisfaction
19	Abdel-Maguid EM (26)	2021	Split-face clinical	Egypt	Fractional CO_2 laser + topical SC-CM or fractional CO_2 laser + saline; fractional CO_2 laser + topical PRP or SC-CM	17 [34]; 16 [32]	33 [66]	–	–	–	3 monthly sessions	–	ECCA, 2 blinded dermatologists
20	Sallam MAE (27)	2021	Split face comparative	Egypt	Microneedling with PRP; fractional CO_2 laser with PRP	20; 20	20 [40]	–	–	–	–	–	GBS
21	Wen X (28)	2020	Randomized split face, investigator-blinded	China	755 nm picosecond alexandrite laser fitted with DLA; within-patient control	16; 16	16 [32]	–	–	–	three treatments at 1-month intervals	–	ECCA, CEAS
22	Pooja T (29)	2020	Randomized	India	Fractional CO_2 laser; microneedling; PRP	20; 20; 20	60	–	Age range of 16–45	–	Monthly intervals for 4 sessions.	–	GBS
23	Mahamoud WA (4)	2020	Split face	Egypt	Fractional CO_2 laser + PRP; fractional carbon dioxide laser + noncross-linked hyaluronic acid	30; 30	30 [60]	14 M/16 F	–	–	3 sessions of full-face fractional CO_2 laser re- surfacing	–	GBS grading system, 2 blinded investigators
24	Lakkireddygari S (30)	2020	Comparitive	India	Fractional CO_2 laser; fractional CO_2 laser + autologous platelet rich plasma	40; 40	80	–	–	–	6 sessions at 1 month intervals	–	Scar score
25	Kwon HH (31)	2020	Prospective, double-blind, randomized, split-face	Korea	Fractional CO_2 laser + human adipose tissue stem cell-derived exosomes; fractional CO_2 laser + control gel	25; 25	25 [50]	–	–	–	–	–	–
26	Kwon HH (32)	2020	Prospective, randomized, split-face, controlled	Korea	1,064-nm neodymium-doped yttrium aluminum garnet picosecond laser using a diffractive optical element; nonablative 1,550-nm erbium-glass laser	25; 25	25 [50]	11 M/14 F	Aged 19–37	–	3-week intervals	8 weeks	ECCA, IGA, patients' reports at the final visit
27	Abdel Kareem IM (33)	2020	Comparative split face	Egypt	Fractional CO_2 laser; fractional CO_2 laser + CO_2gas	–	–	–	17–42	–	–	–	Follow-up photographs, patient satisfaction
28	Kaçar N (34)	2020	Prospective, split-face, single-blinded, controlled clinical	Turkey	Fractional CO_2 lasers; F CO_2 *vs.* FRF + fractional radiofrequency	27; 27	27 [54]	–	–	–	–	–	ECCA, patient satisfaction
29	Chopra A (35)	2020	Comparative	India	Microneedling; fractional CO_2	30; 30	60	–	–	–	Every 4 weeks for a period of 24 weeks	–	Per quantitative global acne scarring classification
30	Chen CJ (36)	2020	Split face, randomized controlled	China	Intense pulsed light; pulsed dye laser	21; 21	21 [42]	–	–	–	2 weeks interval for 4 treatment sessions	–	VISIA data, acne lesion counts, complications, and skin biopsies

Table 1 *(continued)*

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No.	Author	Year	Study design	Country	Intervention	Number of cases [faces]	Total number of samples [faces]	Gender (male/female)	Age, years	Course of the disease	Course of treatment	Follow-up time	Outcome indicator
31	Chayavichitsilp P (37)	2020	Randomized, single-blinded, intrapatient, left-to-right comparative	Thailand	Fractional Nd:YAG 1,064-nm picosecond laser; fractional 1,550-nm erbium fiber laser	30; 30	30 [60]	16 M/14 F	Age ≥18	–	4 times at 4-week intervals	–	ECCA
32	Arsiwala NZ (38)	2020	Hospital-based prospective, doubleblinded, randomized, and comparative	India	PRP + fractional CO_2 laser; fractional CO_2 laser	17; 16	33	21 M/11 F	24.36±4.37	–	–	Follow-up for next laser session every 4 weeks up to 12 weeks	GBS qualitative grading
33	An MK (39)	2020	Randomized controlled split-face	Korea	Topical poly-lactic acid; microneedle fractional radiofrequency	36; 36	36 [72]	–	–	–	–	–	Acne scar assessment score assessment of patient satisfaction
34	Al-Sultany HA (40)	2020	Comparative	Iraq	Fractional CO_2 laser; MFR	21; 21	42	15 M/6 F	20–48, average 36	–	Once monthly for 4 months	–	GBS scale
35	El-Taieb MA (41)	2019	Randomized clinical	Egypt	Fractional erbium-YAG laser; PRP; fractional erbium-YAG laser + PRP	25; 25; 25	75	–	–	–	–	–	GBS, system clinical, assessment clinical improvement, clinical satisfaction
36	Al Taweel AI (42)	2019	Comparative	Egypt	Fractional CO_2 laser + PRP; carboxytherapy + PRP	20; 20	40	–	–	–	–	–	Acne scars, patients' satisfaction
37	Abou Eitta RS (43)	2019	Single-center, split-face, prospective clinical	Egypt	Fractional CO_2 laser; autologous adipose-derived stem cells	10; 10	10 [20]	–	–	–	–	3 months	GBS, scar area percentage, skin function
38	Elsaie ML (44)	2018	–	Egypt	Ablative 10,600 nm CO_2 lasers; nonablative 1,540 nm erbium doped glass laser	29; 29	58	39 M/19 F	Aged 18–45	–	4 treatment sessions with a 3-week-free interval	–	2 blinded dermatologists, subjective assessment
39	Dierickx C (45)	2018	–	Belgium	Picosecond 755 nm alexandrite laser	7; 7	7 [14]	–	–	–	–	–	6-point grading score
40	Abdel Aal AM (46)	2018	Single-blinded, comparative split-face	Egypt	Fractional CO_2 laser; PRP + fractional CO_2 laser	30; 30	30 [60]	–	–	–	–	3 days, 7 days, 1 month, and 3 months after sessions	GBS
41	Saluja SS (47)	2017	Randomized split-face controlled	America	1,550 nm non-ablative fractional laser; oral isotretinoin	10; 10	10 [20]	–	–	–	–		Blinded dermatologist
42	Osman MA (48)	2017	Randomized fplit-face clinical	Egypt	Fractional erbium-doped Yttrium aluminum garnet laser; microneedling	30; 30	30 [60]	20 M/10 F	Aged 21–41	–	–	3 months	Patient satisfaction, clinical assessment
43	Min S (49)	2017	Prospective, single-blind, and comparative (randomized split-face) clinical	Korea	Er: YAG laser; bipolar radiofrequency combined with infrared diode laser	24; 24	24 [48]	–	–	–	–	–	ECCA, 5-point Investigator's Global Assessment
44	Kwon HH (50)	2017	Prospective, randomized split-face	Korea	Non-ablative 1,550-nm Erbium-glass laser + microneedling radiofrequency; microneedling radiofrequency	28; 28	28 [56]	15 M/13 F	–	–	16-week	–	IGA, ECCA
45	Khamthara J (51)	2017	Randomized, split-face, evaluator-blinded, placebo-controlled, comparative	Thailand	Silicone gel; placebo; ablative Er:YAG laser	19; 19	19 [38]	–	–	–	–	–	Subject's evaluation, physicians' global evaluation
46	Faghihi G (52)	2016	Split-face randomized clinical	Iran	Ablative CO_2 resurfacing laser + PRP; ablative carbon dioxide resurfacing laser	16; 16	16 [32]	12 M/4 F	–	–	–	–	–
47	Cachafeiro T (53)	2016	Randomized clinical	Brazil	Non-ablative fractional erbium laser 1,340 nm; microneedling	22; 20	42	–	–	–	–	–	Generalized estimating equation, Mann-Whitney test

Table 1 *(continued)*

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No.	Author	Year	Study design	Country	Intervention	Number of cases [faces]	Total number of samples [faces]	Gender (male/female)	Age, years	Course of the disease	Course of treatment	Follow-up time	Outcome indicator
48	Anupama YG (54)	2016	–	India	Subcision followed by CO_2 laser; CO_2 laser alone	25; 25	50	–	–	–	4 sessions at 4-week interval	–	–
49	Faghihi G (55)	2015	Randomized split-face clinical	Iran	Fractional CO_2 laser; punch elevation combined with fractional carbon dioxide laser	42; 42	42 [84]	–	–	–	–	–	2 dermatologists blinded to treatment
50	Chae WS (56)	2015	Comparative	Korea	1,550 nm Er:Glass fractional laser; fractional radiofrequency microneedle	20; 20	40	–	–	–	–	–	ECCA
51	Yuan XH (57)	2014	Comparison	China	Fractional CO_2 laser (20 mJ, density 10% and the other half with 20 mJ, density 20%); Fractional CO_2 laser (10 mJ, density 10% and the other half with 20 mJ, density 10%)	10; 10	20 [40]	10 M/10 F	Aged 22–31	–	–	–	2 blinded dermatologists self-assessment
52	Rongsaard N (58)	2014	Randomized split-face clinical	Thailand	Fractional erbium-doped glass 1,550-nm; fractional bipolar RF	20; 20	20 [40]	–	Aged 18–55	–	–	–	3 blinded dermatologists, patients evaluated clinical improvement texture scores
53	Leheta TM (59)	2014	Randomized controlled	Egypt	PCI + TCA 20%; 1,540 nm non-ablative fractional laser; 1,540 nm fractional laser + PCI + TCA 20%	13; 13; 13	39	–	–	–	–	–	Scar severity scores
54	Ahmed R (60)	2014	–	Egypt	CO_2 laser without needling; CO_2 laser with needling	30; 30	30 [60]	–	–	–	4 sessions at 3-week interval	3 months	GBS, acne scar severity index, qualitative scarring grading system
55	Zhang Z (61)	2013	Randomized split-face clinical	China	Fractional microplasma radio frequency technology; CO_2 fractional laser	33; 33	33 [66]	–	–	–	–	–	ECCA, patient satisfaction
56	Mohammed G (62)	2013	Randomized clinical	Egypt	CO_2 laser with needling applied; CO_2 laser without needling applied	30; 30	60	–	–	–	Five times at 2- to 3-week intervals	–	Acne scar severity index, GBS, patient satisfaction evaluation score
57	Manuskiatti W (63)	2013	–	Thailand	fractional Er:YAG; CO_2 lasers	24; 24	24 [48]	–	22–51	–	2 treatments with a 2-month interval	1, 3, and 6 months after the final treatment	Two blinded medical assessors, Patient Self-Assessment, Scar Volume Assessment
58	Lee JW (64)	2011	Simultaneous split-face	Korea	Ablative CO_2 fractional + PRP; ablative CO_2 fractional	14; 14	14 [28]	4 M/14 F	28.1 (range, 21–38)	–	–	–	2 different blinded dermatologists
59	Asilian A (65)	2011	–	Iran	Q-Switched 1,064-nm Nd:YAG laser; fractional CO_2 laser	32; 32	64	–	–	–	–	–	Patients satisfaction, physicians' assessment, two blinded dermatologists
60	Alexis A (66)	2011	Prospective, split-face, randomized, controlled	America	1,550 nm erbium-doped fractionated laser [40 mJ and treatment level 4 (11% surface area coverage)]; 1,550 nm erbium-doped fractionated laser [40 mJ and treatment level 7 (20% surface area coverage)]	18; 18	18 [36]	–	–	–	–	–	QGSGSS, blinded investigator global VAS, Skindex-16
61	Mahmoud BH (67)	2010	Prospective, single-blind, randomized	America	1,550-nm fractional laser (10 mJ); 1,550-nm fractional laser (40 mJ)		15	3 M/12 F	–	–	–	–	Blinded evaluators
62	Hedelund L (68)	2010	Randomized controlled	the UK	1,540-nm nonablative fractional laser	5; 5	10	–	18–60	–	–	–	Scar texture, skin colour, patients significance
63	Cho SB (69)	2010	Randomized split-face	Korea	1,550-nm erbium-doped FPS; 10,600-nm CO_2 FS	8; 8	8 [16]	8 M	Mean 21.3, range 20–23	–	–	3 months	Two blinded dermatologists
64	Wanitphakdeedecha R (70)	2009	–	Thailand	VSP Er:YAG laser (300 micros/1,500 micros)	12; 12	24	–	–	–	–	1, 2, and 4 months	Skin smoothness, scar volume

Table 1 *(continued)*

Table 1 *(continued)*

No.	Author	Year	Study design	Country	Intervention	Number of cases [faces]	Total number of samples [faces]	Gender (male/female)	Age, years	Course of the disease	Course of treatment	Follow-up time	Outcome indicator
65	Min SU (71)	2009	Randomized split-face clinical	Korea	Long-pulse Nd:YAG laser; 585/1,064-nm laser + long-pulse Nd:YAG laser	19; 19	19 [38]						ECCA, patient satisfaction
66	Lee DH (72)	2009	Randomized split-face clinical	Korea	PDL; 1,064-nm long-pulsed Nd:YAG laser	18; 18	18 [36]						ECCA
67	Kim HJ (73)	2009	Simultaneous split-face	Korea	1,550 nm erbium: glass fractional laser; chemical reconstruction of skin scars	20; 20	20 [40]						Objective and subjective improvement
68	Yaghmai D (74)	2005	–	America	1,064 nm Nd:YAG laser; 1,320 nm Nd:YAG laser	6; 6	12						Evaluated by photographic and profilometric methods
69	Tanzi EL (75)	2004	Prospective clinical and histologic	America	Long-pulsed 1,320-nm Nd:YAG; 1,450-nm diode lasers	20; 20	20 [40]						Clinical improvement, patient satisfaction scores

PRP, platelet-rich plasma; Nd:YAG, neodymium-doped yttrium aluminium garnet; FTL, fractional non-ablative; Er:YAG, Erbium:Yttrium-Aluminum-Garnet; MFR, microneedling fractional radiofrequency; PCI, percutaneous collagen induction; TCA, trichloroacetic acid; FPS, fractional photothermolysis systems; FS, fractional laser system; VSP, variable square pulse; PDL, pulsed dye laser; ECCA, échelle d'évaluation clinique des cicatrices d'acné; DLQI, dermatology quality of life index; VSS, Vancouver scar scale; GBS, Goodman and Baron; CEAS, Clinician Erythema Assessment Scale; IGA, Investigator's Global Assessment; TEWL, trans-epidermal water loss; MI, melanin index; RF, radiofrequency; SCCM, stem cell-conditioned medium; QGSGSS, Quantitative Global Scarring Grading System Score; VAS, visual analog scale.

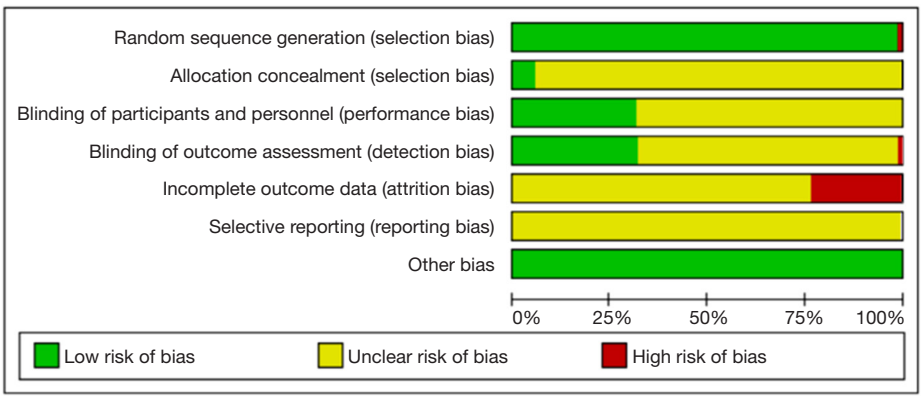

Figure 2 Summary of risk of bias assessment.

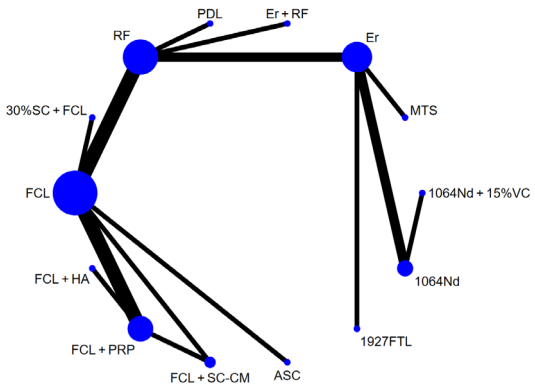

Figure 3 The network of evaluating the effects of different interventions on improving acne scars.

table of random digits was used in 6 studies, computer software in 8 studies, and sequence generation in 1 study. The remaining studies did not report the method of random allocation. Allocation concealment by using closed envelopes was reported in 4 articles. A total of 25 studies used blinding to reduce performance bias, among which 7 studies used double-blinding and 18 used single-blinding. There were 22 studies that used blinding in outcomes measurement to reduce measurement bias, among which 3 studies used single-blinding, 16 used double-blinding, and 3 used triple-blinding. The number of drop-out patients ranges from one to nine (*Figure 2*).

Meta-analysis results

Evaluation of scar improvement

The ECCA and GBS methods were used to evaluate the improvement of acne scars. The standard mean difference (SMD) was used in the meta-analysis.

Some 14 interventions were involved in the 18 included studies (1,6,8,10,12,14,15,17,18,26,32,38,40,43,49,50,56,61), among which 6 were combined therapies [1064Nd + 15%VC, Er + RF, 30%SC + FCL, FCL + PRP, FCL + HA, FCL + SC-CM (stem cell-conditioned medium)] and 8 were monotherapies (1064Nd, Er, FCL, MTS, ASC, RF, 1927FTL, PDL). The network demonstrated the direct or indirect relationship between the 14 interventions. A closed loop was formed by FCL, FCL + PRP, and FCL + SC-CM interventions. The number of studies on FCL ranked the first, followed by the number of studies on Er. The number of studies on comparisons between FCL and FCL + PRP was the highest (*Figure 3*) (laser abbreviations involved in the text are shown in *Table 2*).

According to the SUCRA value, different laser treatments were ranked as follows: FCL + PRP (0.699) > 1064Nd + 15%VC (0.675) > 1064Nd (0.627) > 1927FTL (0.582) > FCL + HA (0.58) > Er (0.576) > Er + RF (0.541) > PDL (0.514) > MTS (0.510) > FCL + 30%SC (0.444) > ASC (0.364) > FCL + SC-CM (0.312) > FCL (0.299) > RF (0.277). It was shown that FCL + PRP (0.699) ranked the first, followed by 1064Nd + 15%VC (0.675). All the interventions were compared with the others using a league table. As shown by Table S2, the improvement of the acne scars was the continuous variable. The confidence intervals (CIs) of most pairwise comparisons included 0, indicating that there was no significance in most pairwise comparisons of the intervention. Compared with FCL, scars were significantly improved after FCL + PRP treatment (SMD: −1.76; 95% CI: −3.49 to −0.03). The ranking of improvement of the acne scars is shown in Table S2. The funnel plot was symmetric, indicating that the publication bias was not significant

Table 2 Laser abbreviations

Treat	Intervention	Abbreviation
Treat 1	Fractional carbon dioxide laser	FCL
Treat 2	30% supramolecular salicylic acid	30%SC
Treat 3	Monopolar radiofrequency	RF
Treat 4	Pulsed dye laser	PDL
Treat 5	Er:YAG laser treatment	Er
Treat 6	Fractional radiofrequency microneedle	MTS
Treat 7	1,064-nm neodymium-doped yttrium aluminum garnet picosecond laser	1064Nd
Treat 8	Fractional non-ablative 1,927 nm thulium laser	1927FTL
Treat 9	Autologous adipose-derived stem cells	ASC
Treat 10	Stem cell-conditioned medium	SC-CM
Treat 11	Platelet-rich plasma	PRP
Treat 12	Non-cross-linked hyaluronic acid	HA
Treat 13	Fractional microneedle	FM
Treat 14	carboxytherapy	CO_2gas

(*Figure 4* and *Figure 5*).

Cure rate

A total of 13 studies (10,12,24,33,41-44,46,48,50,52,56) reported a cure rate. A total of 12 types of interventions were included, of which 7 were combined therapy (CO_2gas + PRP, FCL + CO_2gas, Er + FCL, FCL + 30%SC, FCL + PRP, FCL + yifu, Er + PRP) and 5 were monotherapies (FCL, RF, MTS, PRP, ER). A total of 5 closed loops were formed. The sample size of the studies on FCL was the largest, followed by the studies on Er. There were more studies reporting the comparison of FCL and FCL + PR and comparison of FCL and ER (*Figure 6*).

A ranking table demonstrated the ranking of the cure rates of acne scar by different interventions: Er + PRP (0.873) > FCL (0.773) > FCL + 30%SC (0.772) > FCL + yifu (0.732) > FCL + CO_2gas (0.675) > FCL + PRP (0.641) > Er + FCL (0.449) > CO_2gas + PRP (0.446) > MTS (0.261) > Er (0.217) > RF (0.106) > PRP (0.057), among which Er + PRP (0.873) ranked the first (*Figure 7*).

Table S3 presented that the CI in the pairwise comparison of some interventions included 1. Since the cure rates was a categorical variable, this result indicated that the comparison was non-significant. Compared with FCL, the cure rate of FCL + PRP was increased (SMD: 1.64, 95% CI: 1.17 to 2.28). Compared with PRP, the cure rate of FCL + 30%SC was increased (SMD: 23.97, 95% CI: 1.59 to 361.84). Compared with PRP, the cure rate of Er + PRP was increased (SMD: 21.91, 95% CI: 4.02 to 119.41). Other significant comparisons included FCL *vs.* RF, FCL *vs.* PRP, FCL + yifu *vs.* FCL, FCL + yifu *vs.* RF, FCL + yifu *vs.* PRP, FCL + yifu *vs.* MTS, FCL + yifu *vs.* CO_2gas + PRP, FCL + PRP *vs.* FCL, FCL + PRP *vs.* RF, FCL + PRP *vs.* PRP, FCL + 30%SC *vs.* RF, FCL + 30%SC *vs.* PRP, Er + PRP *vs.* RF, Er + PRP *vs.* PRP, Er + FCL *vs.* FCL, Er + FCL *vs.* RF, Er + FCL *vs.* PRP, Er + FCL *vs.* MTS, Er + FCL *vs.* Er, Er + FCL *vs.* CO_2gas + PRP, Er *vs.* RF, and Er *vs.* PRP. The ranking of the cure rates of acne scar is depicted in Table S3. The risk of bias of the studies was assessed, revealing that most studies were evenly distributed on both sides of the effect size, indicating that the publication bias was non-significant (*Figure 8*).

Satisfaction

There were 8 studies (15,16,24,41,42,44,46,52) that reported satisfaction. A total of 8 types of interventions were included, of which 3 were combined therapy (Er + PRP, FCL + PRP, CO_2gas + PRP) and 5 were monotherapies (FCL, 1064Nd, Er, PRP, RF). A total of 3 closed loops were formed. The sample size of the studies on FCL was the largest, followed by the studies on FCL + PRP. There were more studies reporting the comparison of FCL and FCL + PRP (*Figure 9*).

The interventions were ranked according to SUCRA values: FCL (77.2) > PRP (0.649) > CO_2gas + PRP (0.530) > Er + PRP (0.524) > FCL + PRP (0.423) > 1064Nd (0.393) > Er (0.364) > RF (0.346) (*Figure 10*).

The pairwise forest plot and Table S4 showed the comparison between any 2 interventions (*Figure 5*). The CI of all the comparisons included 1. Since satisfaction was a categorical variable, the results indicated that all the comparisons were non-significant.

The funnel plot presented that the distribution of the studies was mostly symmetrical, indicating a non-significant publication bias (*Figure 11*).

For the safety of each laser intervention method, there will be a certain degree of complications, such as erythema, edema, pigmentation, exudation, purpura, pain, and so on. These complications are diverse, and the complications of different intervention methods are also different, which can not be uniformly evaluated.

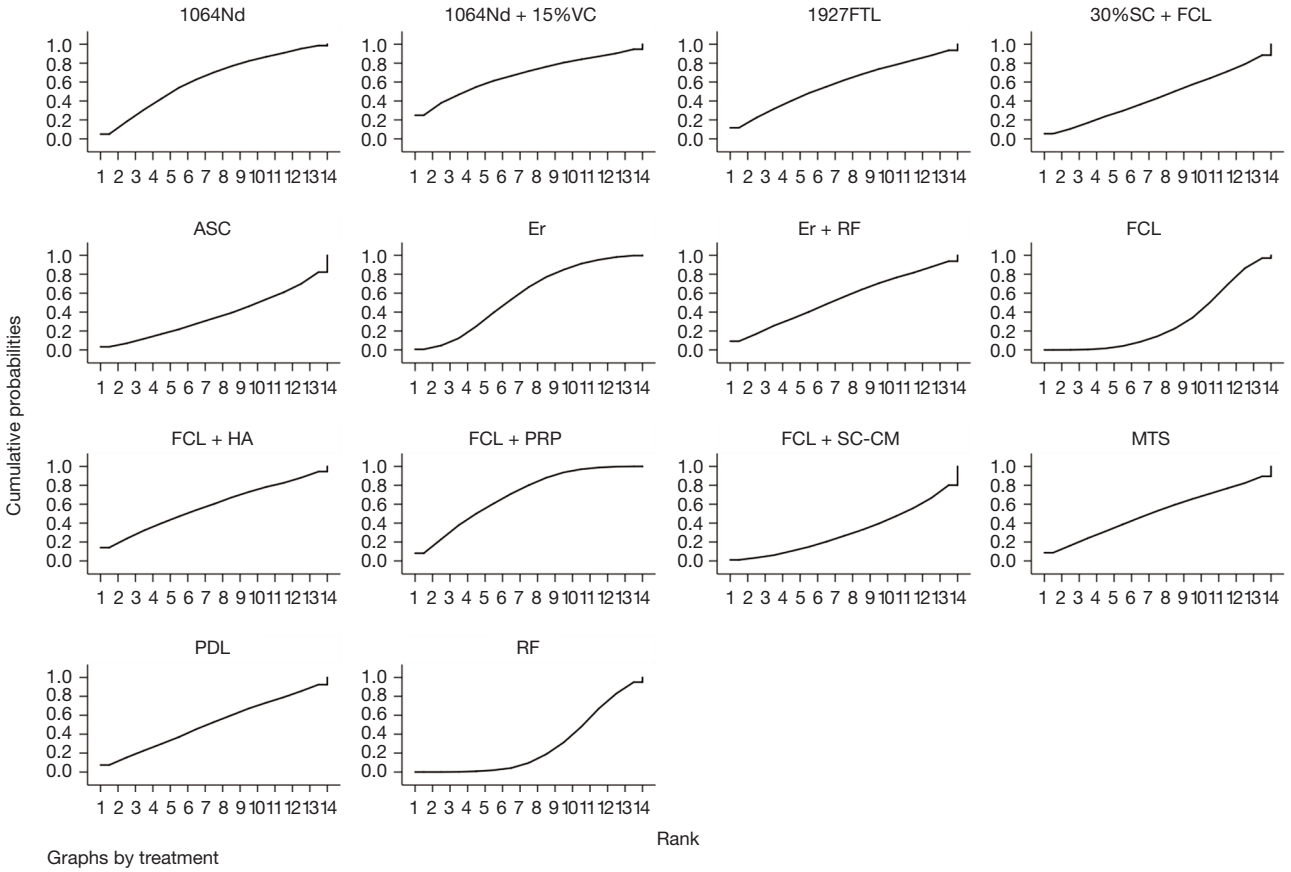

Figure 4 The SUCRA of evaluating the effects of different interventions on improving acne scars. SUCRA, surface under the cumulative ranking curve.

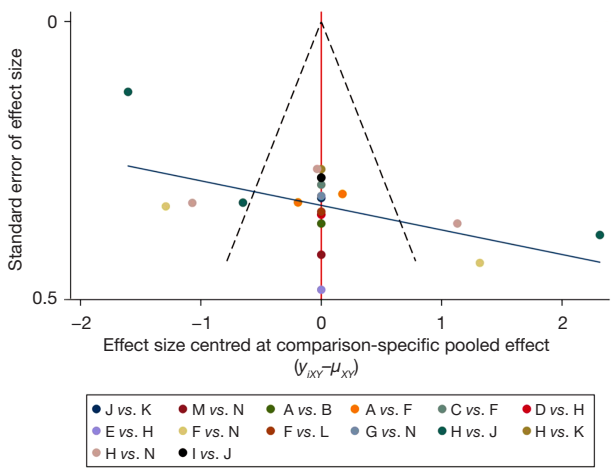

Figure 5 The funnel plot of evaluating the effects of different interventions on improving acne scars. A: 1064Nd; B: 1064Nd + 15%VC; C: 1927FTL; D: 30%SC + FCL; E: ASC; F: Er; G: Er + RF H: FCL; I: FCL + HA; J: FCL + PRP; K: FCL + SC-CM; L: MTS; M: PDL; N: RF.

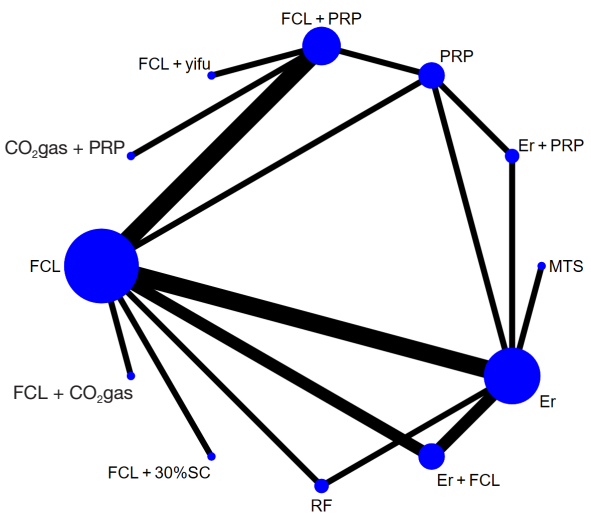

Figure 6 The network on the cure rate of different interventions.

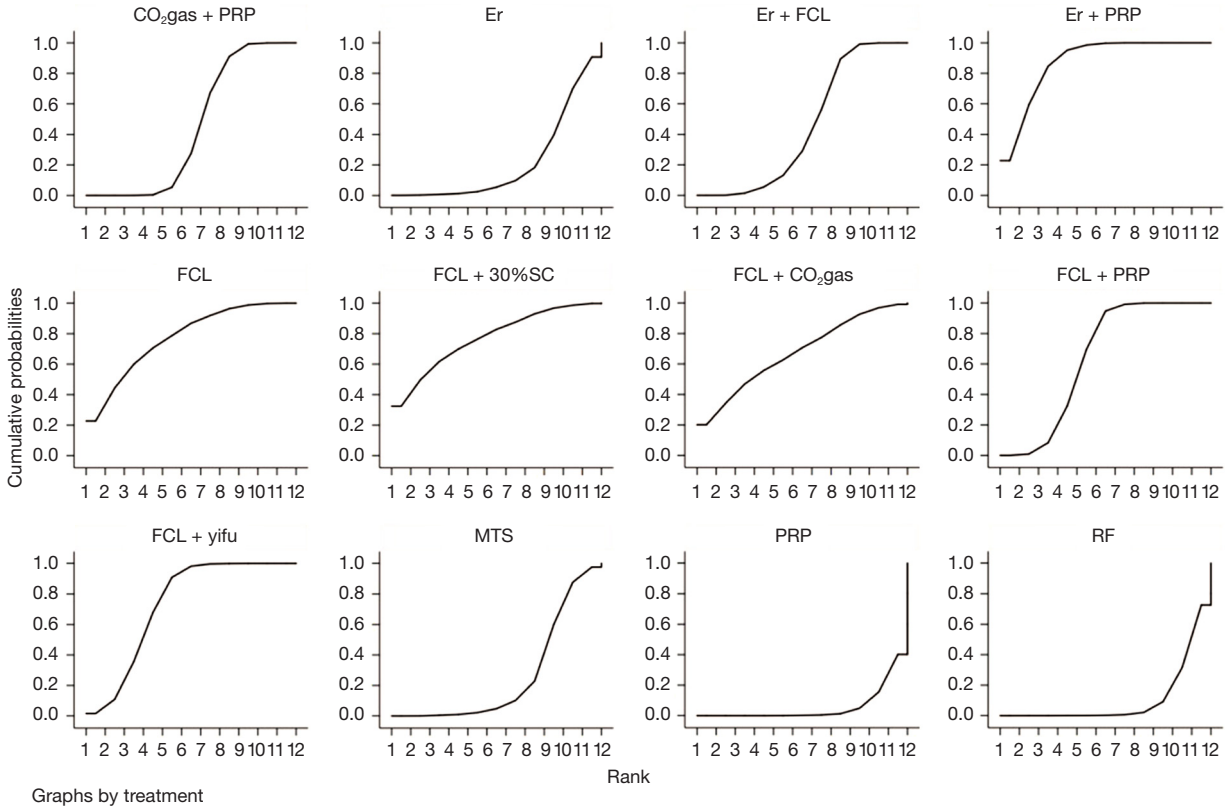

Figure 7 The SUCRA of evaluating the cure rate of different interventions. SUCRA, surface under the cumulative ranking curve.

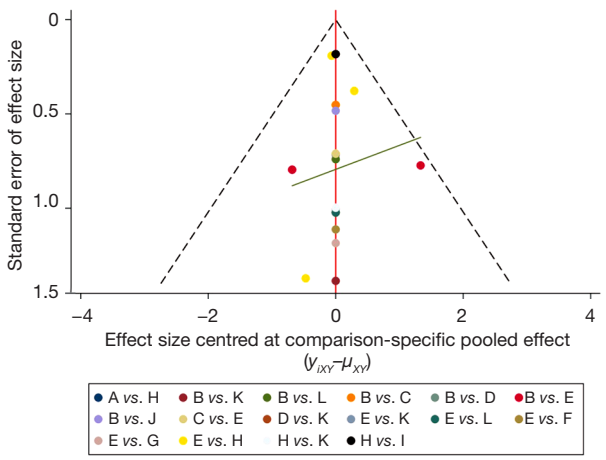

Figure 8 The funnel plot of evaluating the cure rate of different interventions. A: CO_2gas + PRP; B: Er; C: Er + FCL; D: Er + PRP; E: FCL; F: FCL + 30%SC; G: FCL + CO_2gas; H: FCL + PRP; I: FCL + yifu; J: MTS; K: PRP; L: RF.

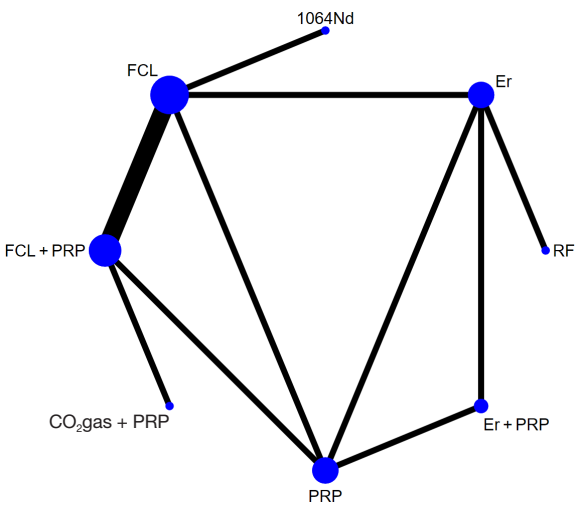

Figure 9 The network of evaluating patients' satisfaction after treatment for acne scars.

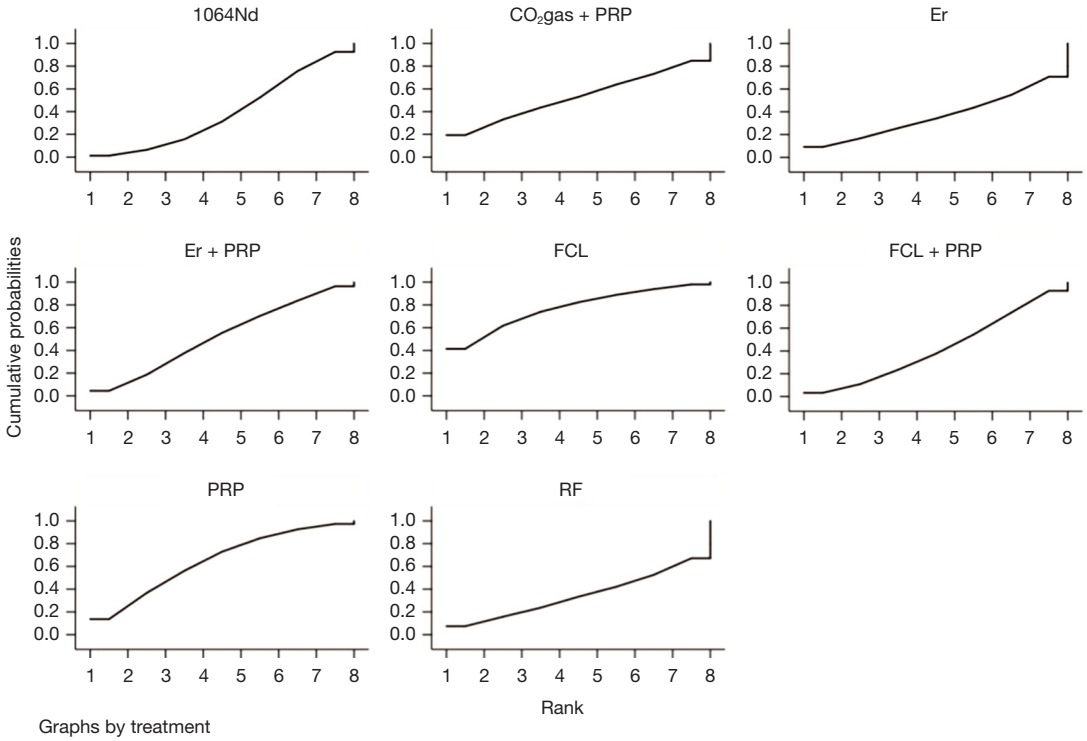

Figure 10 The SUCRA of evaluating patients' satisfaction after receiving different interventions for acne scars. SUCRA, surface under the cumulative ranking curve.

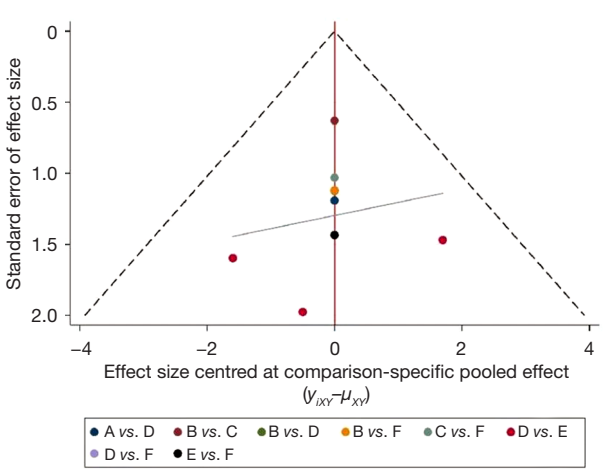

Figure 11 The funnel plot of evaluating patients' satisfaction after receiving different interventions for acne scars. A: 1064Nd; B: CO_2gas + PRP; C: Er; D: Er + PRP; E: FCL; F: FCL + PRP.

Discussion

There are various options for treating acne scars. Laser treatment, a non-invasive method, has gradually become a mainstream choice with the maturity of optoelectronic technology and the invention of various laser devices. Therefore, we conducted this network meta-analysis to directly or indirectly compare the effects of multiple interventions on acne scarring. A focus of this study was to determine the most effective methods of treating acne scars. The top 3 treatments were Er + PRP, FCL monotherapy, and FCL + 30%SC. The most effective method was Er laser + PRP, which might be attributed to the 2 modes of Er (short-pulsed and dual-mode Er:YAG) (76). Furthermore, the commonly used wavelength of Er laser is 2,940 nm, and its peak absorption coefficient of Er for water is higher than that of FCL (48). A previous meta-analysis compared FCL and Er laser and found that there was no significant difference in efficacy between the 2 devices and both were effective in the treatment of acne scarring (77). This is also the reason why acne scars can be effectively treated. PRP has a synergistic effect with Er to maximize the cure rate. Currently, there is a lack of meta analyses comparing Er with other laser treatments. A 30% salicylic acid concentration can increase the efficacy of FCL, which may reduce the repeat times of laser treatments. This

indicates that salicylic acid can achieve better therapeutic effects with fewer laser treatments. The economic burden can be reduced for patients without increasing pain and adverse reactions (6). However, this study found that there was no difference in the cure rate between FCL and FCL + 30%SC, indicating that 30%SC might only be advantageous in increasing the efficiency of laser for 1 time. The cure rate of FCL could not be increased generally. This result should be validated by further research with extended follow-up time and larger sample size. As for the improvement of acne scarring assessed by ECCA and GBS scales, the top 3 treatments were FCL + PRP, 1064Nd + 15%VC, and 1064Nd monotherapy. There were RCTs (22) and meta-analyses (78) showing that FCL + PRP was better than FCL monotherapy in treating acne scars. There were also meta-analyses comparing FCL with other treatments (9). FCL + PRP has gradually become one of the most important treatments for acne scars. However, there is a lack of meta analyses comparing FCL + PRP with other treatments. Therefore, there is no evidence on the relationship between FCL + PRP and other treatments to support the results in our study. There were RCTs demonstrating that 1064Nd had the same efficacy as FCL in the treatment of atrophic acne scars (16). Although they were both combined therapies, this study showed that FCL + PRP had better effects on the improvement of acne scars compared with 1064Nd + 15%VC. In the treatment for atrophic acne scars, long-pulse Nd:YAG 1064 nm laser + 15% vitamin C solution (ascorbic acid) was more effective in reducing GBS scores compared with long-pulse Nd:YAG 1064 nm laser monotherapy, which was consistent with the results in our study. However, no study had investigated whether there is difference in the efficacy between the combined therapy and 1064Nd monotherapy (18). This requires extensive long-term research for more comprehensive results. According to our analysis, in terms of patient satisfaction, the top 3 treatments were FCL, PRP, and CO_2gas + PRP. A previous meta-analysis compared FCL with other laser treatments and the results showed that the efficiency of FCL was much higher than that of other treatments (9) in treating acne scars. The improvement of appearance was a key reason for increased patient satisfaction. The cure rate of FCL was less than that of FCL + PRP (26). However, intradermal injection into the inflammatory skin (due to prior treatment with FCL) could lead to worsening pain (22), which might greatly influence patient satisfaction. Patients may ignore the treatment effect due to intense pain and feel more satisfied with FCL monotherapy. Efforts are still required to balance the treatment effect and adverse reactions in clinical practice. Although PRP is a non-laser method and its efficacy is inferior to that of laser treatment or combination therapy, it has the advantages of simple operation, short recovery time, and low cost compared with other non-laser treatment (22). These benefits are the reasons why patients prefer PRP treatment. A previous study has also demonstrated that although the efficacy of CO_2gas + PRP was worse than that of FCL + PRP, the complications of CO_2gas + PRP were less compared with FCL + PRP, which led to significantly higher satisfaction of patients who received CO_2gas + PRP (42).

There were some limitations to our study. On the one hand, the present study did not explore whether various treatments have varied therapeutic effects on patients of different genders, skin colors, and skin types. According to a report, women visit dermatologists for acne scars more frequently than men, and darker skin is more likely to cause complications (43). Furthermore, the effect of laser treatment varies on patients with different skin types. For instance, CO_2 laser is more effective for rolling and boxcar scars than icepick scars. (boxcar scars are round or oval sunken scars that have relatively sharp edges with a diameter of 1.5 to 4 mm; rolling scars are wavy, greater than 4 mm in diameter, and have soft edges; icepick scars feature a V-shape, deep lesions, a diameter of less than 2 mm, and sharp edges) (4). However, the included studies did not classify patients by gender, skin color, and skin type. On the other hand, the follow-up duration in the included studies was relatively short. A study has reported an increase in the quantity and density of collagenous fiber in the dermal papilla for up to 8 weeks after laser treatment. Therefore, there may be a difference in the data obtained.

Conclusions

Combination therapy is recommended for acne scars. The combination of Er with PRP has the highest cure rate for acne scars, followed by FCL combined with 30%SC, or single FCL. FCL in combination with PRP improves acne scars most significantly, and 1064Nd combined with 15%VC is also effective. In contrast, patients prefer single treatment, with single FCL as the most satisfying option, followed by single PRP. This may be associated with their feelings about treatment, side effects, and costs. Therefore, Er + PRP and FCL + PRP can be used as the first choice for clinical treatment of acne scars. Additionally, using FCL

alone is also an effective and elective treatment method due to its affordable cost and comfort.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-NMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5997/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5997/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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