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REVIEW

Platelet-rich plasma in the treatment of scars, to suggest or not to suggest? A systematic review and meta-analysis

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Abstract

Despite the rising trend for applying platelet-rich plasma (PRP) in the management of various types of scars, there is no convincing evidence supporting its use. This motivated us to review the randomized clinical trials that examine the effectiveness and safety of PRP, alone or in combination with other methods, for the management of atrophic or hypertrophic/keloidal scars. The Web of Science, Scopus, Google Scholar, and Cochrane Library databases were systematically searched until September 1st, 2020. Thirteen clinical trials were enrolled in the meta-analysis, and 10 more were reviewed for their results. The random effect meta-analysis method was used to assess the effect size of each outcome for each treatment type, and I^2 was used to calculate the statistical heterogeneity between the studies. Patients treated with PRP experienced an overall response rate of 23%, comparable to the results seen with laser or micro-needling (22% and 23%, respectively) When used alone, moderate improvement was the most frequently observed degree of response with PRP (36%) whereas, when added to laser or micro-needling, most patients experienced marked (33%, 43%, respectively) or excellent (32% and 23%, respectively) results. Concerning the hypertrophic/keloid scars, the only study meeting the required criteria reported a better improvement and fewer adverse effects when PRP was added to the intralesional corticosteroids. Platelet-rich plasma appears to be a safe and effective treatment for various types of atrophic scars. In addition, when added to ablative lasers or micro-needling, it seems to considerably add to the efficacy of treatment and reduce the side effects.

KEYWORDS

acne scar, atrophic scar, hypertrophic scar, keloid, laser, micro-needling, platelet-rich plasma, PRP, scar, subcision

1 | INTRODUCTION

Scars are the result of the natural wound healing process. The ultimate look of a scar is a function of factors such as the individual's genetic constitution, the type, and severity of the injury, the scar location, etc. An insult to the skin is followed by hemostasis, inflammation, proliferation, and remodeling of the injured tissue (Fabbrocini et al., 2010). The final result is not always cosmetically acceptable. In addition, a deviation from the normal in any of the wound healing stages can lead to abnormal tissue formation. For

example, increased extracellular components can lead to keloid or hypertrophic scar formation, whereas a decrease in these elements results in atrophic scars (Fabbrocini et al., 2010; Goodman, 2000). Scars are often associated with esthetic, functional, and/or psychological issues and may adversely affect a person's quality of life (Bijlard et al., 2017; Tan et al., 2022).

Atrophic scars are skin depressions mainly caused by the destruction of epidermis, dermis, and/or subcutaneous tissue. Tethering the dermis to the underlying layers via various pathological processes can also contribute to the depressed look of these scars (Fabbrocini et al., 2010). Acne, Steria distensa, trauma, surgery, inflammatory conditions such as cutaneous lupus erythematosus, and infections processes such as ecthyma, varicella, and leishmaniasis of the underlying causes. Contrarily, hypertrophic and keloid scars are characterized by excessive tissue formation, that is, disproportionate deposition of collagen and other extracellular matrix (ECM) elements within the dermis (Bran et al., 2009; Brown & Bayat, 2009; Shih & Bayat, 2010; Sidgwick & Bayat, 2012). Unlike hypertrophic scars, keloids progress beyond the scar limits encroaching upon the surrounding healthy-looking skin, and typically do not regress over time. Studies point to the high psychological burden of keloids due to undesirable appearance and functional limitations (Bijlard et al., 2017).

Apart from controlling the primary condition, many methods have been introduced to enhance the appearance of atrophic scars (Behrangi et al., 2020; Golnaz et al., 2019; Goodarzi et al., 2020; Seirafianpour et al., 2021). Provoking new ECM synthesis through controlled destruction of skin layers, reshaping of the affected area via scar excision, skin flaps, grafts, and injection of filling materials are to name but a few. No single option is the perfect solution, and usually, a combination of various treatment modalities is needed to gain acceptable results. Treatment of hypertrophic or keloidal scars is as challenging. Methods include tissue excision, ablative measures, and agents impeding or reversing tissue growth.

Since its introduction in the 1970s by hematologists to treat thrombocytopenia, platelet-rich plasma (PRP) has been put into use for many other medical indications (Zhang et al., 2018). It contains a variety of growth factors such as transforming growth factor-beta 1 (TGFB1), platelet-derived growth factor, vascular endothelial growth factor, brain-derived neurotrophic factor, and insulin-like growth factor 1 making it a tempting option for many medical conditions that rationally seem to benefit from these factors (Andia & Abate, 2013).

The search for finding new therapeutic options for scars has never stopped, as any of the current treatment options are ideally effective. Topical application or intralesional injection of PRP for enhancing atrophic scars is a relatively novel approach with promising results in the preliminary studies. Furthermore, some clinicians have recently started adding PRP to the therapeutic regimens for hypertrophic/keloidal tissues. However, studies with convincing results are expectedly rare.

To the best of our knowledge, this study is the only review and meta-analysis on the studies assessing PRP's efficacy and safety in treating atrophic and hypertrophic/keloidal scars.

2 | METHOD

2.1 | Search strategy

We conducted a systematic review of the literature from the January 1st, 2010 to before September 1st, 2020, in the electronic databases of PubMed, Web of Sciences, Scopus, Google Scholar, and Cochrane Library with no limits to find all the studies that examined the effect of PRP on atrophic and hypertrophic/keloid scars. Search keywords were (Scar OR Keloid OR Keloidal Scar OR Hypertrophic scar Or Atrophic scar Or Acne scar or Striae OR Stretch mark OR traumatic scar) AND (PRP OR PRP) AND (Treatment OR Safety OR Efficacy OR Effectiveness) for the outcome. The search strategy for each database was reported in Appendix 1. All clinical trial papers indexed in English were collected. In addition, studies references were manually reviewed for the related documents not found in the search.

2.2 | Inclusion and exclusion criteria

This study was designed, conducted, and reported based on the Guideline Checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The inclusion criteria were defined using the Population, Intervention, Comparison, results, and Study design approach.

Clinical trials comparing PRP with ablative lasers, microneedling, or subcision, for the treatment of atrophic scars were included in this analysis. The patients were at least 18 years old, and the result was scar improvement. Review studies, letters, editorials, case reports, studies using duplicated data, studies having no control group, and in vitro or ex vivo studies were excluded.

2.3 | Study selection

Two authors (Zahra Ebrahimi, Mahboobeh Kamali) independently reviewed the eligibility of all papers by studying the title, abstract, and, if necessary, their full texts. The third independent researcher (Azadeh Goodarzi) resolved the issue in case of disagreement. The number of excluded articles was recorded along with the exclusion reasons.

2.4 | Data extraction

Data from the eligible studies, including the first author's last name, publication year, study location, sample size, type of scar and Goodman severity, PRP preparation, the combination of treatment, assessment index, follow up time, and adverse effects were extracted using a pre-designed checklist form, independently by two researchers (MJ, AG). The findings were then compared to ensure data validity and reproducibility. If the collected data were different, the

article was discussed in the group of researchers, and the required information was re-evaluated.

To calculate the effect size for the meta-analysis, descriptive data regarding the intervention regimens of fractional laser, a fractional laser with PRP, micro-needling, micro-needling with PRP, and PRP were extracted from the included studies. The response rate was calculated using the proportion of patients in the included studies that showed poor, moderate, marked, or excellent improvement with a confidence interval of 95%.

2.5 | Risk of bias assessment

The quality of the studies was assessed with the help of a modified version of the Downs and Black checklist (Downs & Black, 1998). This 27-item checklist evaluates the standard of reporting of studies, their random error (power of analysis), external validity (selection bias), and internal validity (information bias). The power was either sufficient (score 1) or insufficient (0 scores). When assessing the power of the studies, we determined whether the selected sample size by a certain study was based on an effect size of 0.2, an acceptable probability of type one error of 0.05, and the use of a two-tailed test. The total score for different studies ranged from 0 to 31. Several studies have previously assessed the validity and reliability of this checklist (Hootman et al., 2011). Two authors performed the quality assessment separately, and discords were resolved in group discussions.

2.6 | Data analysis

Our outcomes of interest were the proportions of poor, moderate, marked, and excellent results within each intervention group. The random-effect model was used to calculate the effect size of each outcome. The I^2 (I square) statistics test assessed the heterogeneity of included study results (Higgins et al., 2003). Heterogeneities of <25%, 25%–50%, 50%–75% and >75% were categorized as no, low, moderate and high heterogeneity, respectively. Also, sensitivity analysis was conducted to test the robustness of the pooled effect sizes. Begg's rank correlation and Egger's linear regression tests were run to detect potential publication bias (Begg & Mazumdar, 1994; Egger et al., 1997). All statistical analyses were performed using Stata software (version 16.0, Stata Corporation, College Station, Texas, USA). All analyses were two-tailed, with $p < 0.05$ considered statistically significant.

3 | RESULTS

Five hundred and seventy-nine papers were extracted from PubMed, Scopus, Web of Sciences, Embase, Cochrane, Ovid, and ProQuest in the primary search. Two hundred 63 papers were removed due to duplication. Of the remaining 316, 240 were excluded after evaluating their titles and abstracts, and another 51 were removed following assessing their full texts due to unrelated topics, study types, or outcomes (Figure 1). Finally, 23 Studies were selected for the review, among which 13 were enrolled in the meta-analysis. Twenty-two papers evaluated different treatment modalities for atrophic scars. Only one study on Keloid/hypertrophic scar met the inclusion criteria to enter our review. It was not included in the meta-analysis but will be discussed later.

The results of treatment with laser, laser and PRP, micro-needling, micro-needling, and PRP, and PRP alone were evaluated, respectively from six (Abdel Aal et al., 2018; Agamia et al., 2020; El-Taieb et al., 2019; Faghihi et al., 2016; Galal et al., 2019; Gawdat et al., 2014), five (Abdel Aal et al., 2018; El-Taieb et al., 2019; Faghihi et al., 2016; Galal et al., 2019; Gawdat et al., 2014), four (Asif et al., 2016; El-Domyati et al., 2018; Elfar & Hasby, 2020; Ibrahim et al., 2017), six (Asif et al., 2016; El-Domyati et al., 2018; Elfar & Hasby, 2020; Gawdat et al., 2014; Ibrahim et al., 2017; Nofal et al., 2014), and five (El-Taieb et al., 2019; Elfar & Hasby, 2020; Hodeib et al., 2018; Ibrahim et al., 2017; Nofal et al., 2014) out of 13 articles.

3.1 | Studies and patients' characteristics

Table 1 summarizes the participant studies' characteristics, follow-up results, types of scars, treatment regimens, and treatment side effects. The included studies were clinical trials performed on atrophic acne scars, with sample sizes ranging between 14 and 90. Platelet-rich plasma was administered intradermally in 15 studies and topically in 9. Studies were conducted in four different countries namely, Iran (Faghihi et al., 2016), India (Arsiwala et al., 2020; Asif et al., 2016; Chawla, 2014; Deshmukh & Belgaumkar, 2019; Gawdat et al., 2014; Kar & Raj, 2017), Egypt (Abdel Aal et al., 2018; Abdel-Maguid et al., 2019; Agamia et al., 2020; Bhargava et al., 2019; El-Domyati et al., 2018; El-Taieb et al., 2019; Elfar & Hasby, 2020; Galal et al., 2019; Hassan et al., 2020; Hewedy et al., 2020; Hodeib et al., 2018; Ibrahim et al., 2017; Nofal et al., 2014), and South Korea (Lee et al., 2011; Min et al., 2018).

The age of patients ranged from 16 to 52 years old, with most patients being in their twenties or thirties. The proportion of men ranged from 20 to 71% in different studies, with an average of 42% in total. Most of the treated patients had a skin phototype of III to IV. In most studies, treatment results were assessed 1–4 months after the last treatment session, ranging between zero to 12 months. Fifteen out of 22 studies were split-face.

3.2 | Quality assessment

Table 2 shows the quality assessment results and the risk of bias in the studies assessed by the meta-analysis. All studies are of moderate to good quality (min = 20, max = 23). Four reported their

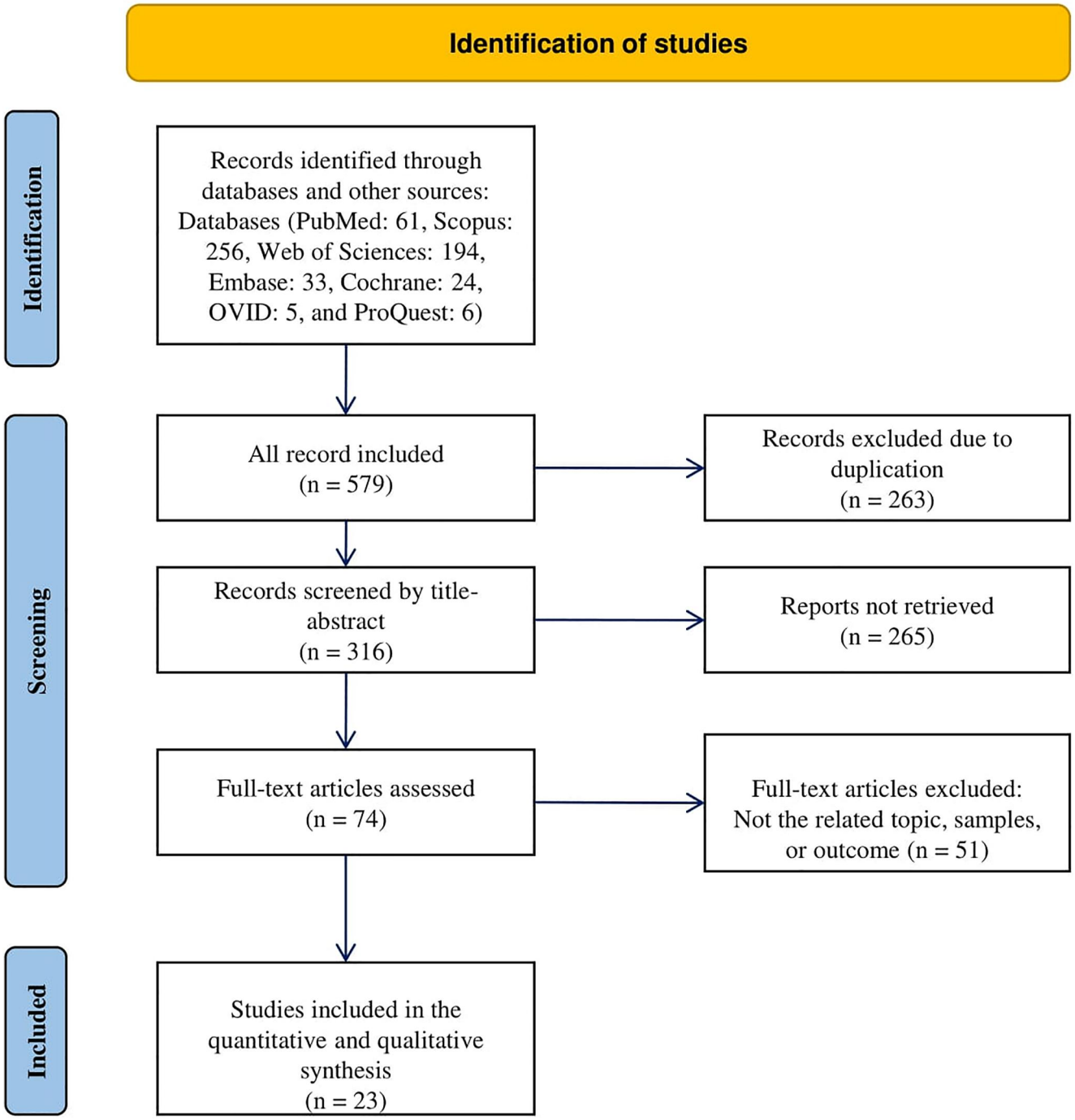


FIGURE 1 Flow diagram showing the process of study inclusion and exclusion

allocation concealment (Agamia et al., 2020; El-Taieb et al., 2019; Elfar & Hasby, 2020; Galal et al., 2019). In 10 studies, the participants were blinded to the intervention (Abdel Aal et al., 2018; El-Domyati et al., 2018; El-Taieb et al., 2019; Elfar & Hasby, 2020; Faghihi et al., 2016; Gawdat et al., 2014; Hassan et al., 2020; Hodeib et al., 2018; Ibrahim et al., 2017; Nofal et al., 2014). In six of these, also the clinicians were unaware of the type of the intervention (double-blind). (Abdel Aal et al., 2018; El-Domyati et al., 2018; El-Taieb et al., 2019; Elfar & Hasby, 2020; Faghihi et al., 2016; Nofal et al., 2014).

3.3 | Analytical results

As mentioned before, meta-analysis was performed merely on the studies evaluating atrophic scars (Figure 2). Results are summarized in Table 3.

The overall response rates were negligibly the same among various interventions. Around 22%–23% of patients showed at least some improvement, that is, poor to excellent responses, to any PRP single-therapy, PRP and micro-needling, PRP and ablative laser therapy micro-needling or ablative laser therapy alone.

TABLE 1 Study characteristics of systematic review

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
1	Elfar and Hasby (2020)	Atrophic acne scars	No	60	Patients were randomized into three groups, four treatment sessions at 4-week intervals:	Intradermal	Dermaroller, 2 mm deep	-Goodman and Baron qualitative	Follow-up at 4 weeks:	Pain, erythema, and edema in groups 2 and 3
		Goodman score: 2–4			1) plasma gel (20 patients)			-Quartile grading scale	-Group 1 exhibited better response than group 2 ($p1 = 0.008$)	
					2) derma roller (20 patients)				-Group 3 showed better efficacy than group 1 3 months after the last session ($p2 = 0.009$)	
					3) plasma gel + derma roller (20 patients)				-Excellent response was noted in 60% of patients with Boxcar scars and in 71.4% of patients with rolling scars	
2	N. Agamia et al. (2020)	Post-traumatic atrophic scars	No	45	Patients were randomized into three groups	Topical	-Fractional Erbium-Doped yttrium aluminum garnet (er: YAG) laser (2940 nm)	-Goodman and Baron qualitative	Follow-up at 1 month:	-Moderate erythema and edema were reported 24–48 h following micro-needling and 3–5 days after laser.
		Severity not mentioned			1) Microneedling + PRP, four sessions at 4-week intervals (15 patients)		-Microneedling, 2–2.5 mm deep	-Quartile grading scale	-Marked improvement in 10, 8, and 5 patients, and moderate improvement in 5, 6, and 5 patients in groups 3, 2, and 1, respectively. Also, one patient in group 2 and 5 patients in group 1 showed mild improvement.	-Superficial crusting in er: YAG group
					2) Microneedling + PRP, six sessions at 4-week intervals (15 patients)				-With the laser, all of the patients showed improvement after four sessions. With micro-needling, all patients showed improvement after six sessions.	-Pain was reported with both methods but was significantly greater with er: YAG laser
					3) Fractional er: YAG laser, four weekly sessions (15 patients)				-Histopathological assessment (H&E, trichrome, and orcein staining)	-PIH in several patients in groups 2 and 3 with skin phototype IV.

(Continues)

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
									revealed statistical significance in all groups. But histopathological parameters were not significantly different between group 1 and group 2.	
3	Arsiwala et al. (2020)	Atrophic acne scars	No	33 (25 patients completed the study)	Patients were randomized into two groups, three monthly sessions:	Topical	Fractional carbon dioxide (CO_2) laser (FCL) (10,600 nm)	-Goodman and Baron qualitative	Follow-up at 1 month after the last session:	-Erythema, edema, pain, and hyperpigmentation observed
		Goodman score: 3–4			1) Fractional CO_2 laser + PRP (17 patients)			-Goodman and Baron quantitative scoring chart	-The mean change was significantly greater in group 1 (4.17) compared with group 2 (3.15).	-Pain and hyperpigmentation were more severe in group 2
					2) Fractional CO_2 laser (16 patients)			-Patient satisfaction	-The mean scar score reduced significantly from 11.5 to 4, in group 1 and from 12 to 3 in group 2 ($p < 0.0001$)	
								-Visual analog scale (VAS)	-The mean VAS improvement was higher in group 1 (4.08) compared with group 2 (3.46). However, this was not significant.	
									-The change in scar score was 4.2, 3.89, and 2.33 for rolling, boxcar, and ice pick scars, respectively. The differences were statistically significant.	

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
4	Galal et al. (2019)	Atrophic acne scars	Yes	30	Three monthly sessions: 1) Fractional CO_2 laser on one side of the face 2) Fractional CO_2 laser + PRP	Intradermal	SmartXide DOT fractionated CO_2 laser (FCL)	-Goodman and Baron qualitative -Quartile grading scale -Patient satisfaction	Follow up every 3 months for 1 year: -The combined fractional CO_2 laser and PRP showed more significant improvement and better results -The goodman global score average before the treatment was 5.7 and decreased to 3.3 and 2.2 following treatment with FCL and FCL + PRP, respectively ($p = 0.0001$) -Significant improvement was observed in scar depth on both sides of the face -The best improvement noticed in rolling and ice pick scars	All the patients reported erythema, edema, and crust formation, 5–7 days after the sessions in group 1 and within 3 days in group 2
5	El-Taieb et al. (2019)	Atrophic acne scar Mild to severe	No	75	Patients were randomized into three groups 1) PRP, 12 sessions at 2-week intervals (25 patients) 2) erbium-YAG laser, six sessions at 4-week intervals (25 patients) 3) Six sessions of erbium-YAG laser plus 12 sessions of PRP over the same period (25 patients)	Intradermal	Erbium-YAG laser (2940 nm)	-Goodman and Baron qualitative -Quartile grading scale -Patient satisfaction	Follow-up at the end of the treatments -Combination therapy resulted in significantly greater improvements than either of the treatments in scar score and clinical appearance.	Erythema, PIH, eruption no significant difference was observed between groups

(Continues)

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
6	Abdel-Maguid et al. (2019)	Atrophic acne scars	Yes	33	Three monthly sessions	Topical	-Amniotic fluid-mesenchymal stem cell-conditioned medium)	-Goodman and Baron qualitative	Follow-up monthly and 3 months after treatment:	-Transient erythema and mild edema on both sides of the face in all patients, within 2–3 days and crust formation for 5 days.
		Goodman score: 3–4			1) Fractional CO_2 laser + topical stem cell-conditioned medium on the right side and fractional CO_2 laser + saline on the left side (17 patients)		-Fractional ablative CO_2 (10,600 nm)	-Quartile grading scale	There is no significant difference in the improvement of acne scars between the fractional CO_2 laser + PRP side and the fractional laser only side ($p = 0.63$). But the, faster and better improvement was observed on the laser + PRP side compared to the laser + SC-CM side ($p = 0.006$)	-PIH was recorded in one patient on both sides of the face in group 1
					2) Fractional CO_2 laser + topical PRP on the right side and fractional CO_2 laser + topical stem cell-conditioned medium on the left side (16 patients)			-Patient satisfaction	-The mean ECCA score showed no significant difference between the sides in either group ($p = 0.676$ and $p = 0.761$)	
								-Histological and quantitative molecular analysis	The ECCA score exhibited a significant reduction in both groups compared with the baseline on both sides of the face.	
								-Echelle d'Evaluation clinique des cicatrices d'acnè (ECCA) scale	-No significant difference was observed between the sides in group 1. In group 2, however, there was a better improvement on the FCL+PRP side ($p = 0.033$)	

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
7	Bhargava et al. (2019)	Atrophic acne scar	No	30	Patients were randomized into two groups, three sessions at 3-week intervals:	Topical	-Subcision using an 18-gauge needle (1.5 mm needle size)	-Goodman and Baron qualitative	Follow-up after 3 months:	-Erythema/edema
		Goodman score: 4			1) Subcision (15 patients)			-Quartile grading scale	-The improvement was more significant for group 2 patients than for group 1 ($p = 0.025$)	-The duration of adverse events was shorter in group 2 than in group 1 (16.1 vs. 32.9 h)
					2) Subcision + needling + PRP (15 patients)			-Patient satisfaction	-Also more significant grade improvement in group 2 ($p = 0.195$)	
8	Hassan et al. (2020)	Atrophic acne scar	Yes	30	Three monthly sessions:	Intradermal	-Subsection (18-gauge, 1½- inch NoKor Admix needle was used)	-Goodman and Baron qualitative	Follow-up after 3 and 6 months	Bumps, PIH, and bruising, especially on the combination therapy side
		Goodman score: 3, 4			1) PRP on one side of the face			-Quartile grading scale	-There was no significant difference between the treated groups, but the side treated with PRP alone showed better improvement.	
					2) subcision + PRP on the other side			-Patient satisfaction	-The best improvement was observed 6 months after treatment with PRP alone	
									-Both procedures improved the skin texture	
9	El-Domyati et al. (2018)	Atrophic acne scars	Yes	24	Patients randomized into 3 groups, 6 sessions at 2-week intervals:	Topical	-Microneedling, 1.5 mm deep	-Dermatologist assessment	Evaluation at baseline, after 1 month of treatment [2 sessions], and after 3 months of treatment	Erythema reported in all groups after 2 days
					1) microneedling + PRP (right side) and microneedling (left side) (8 patients)		-TCA 15%	-Histopathological assessment	-Better response to treatment with microneedling + PRP compared with microneedling single-therapy	
					2) microneedling + TCA (left side) and				-Better response to treatment with	

(Continues)

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
					microneedling (right side) (8 patients)				microneedling + TCA than with microneedling single-therapy	
					3) microneedling + PRP (right side) and microneedling + TCA (left side) (8 patients)				-No difference between the two arms in group 3	
10	(Ibrahim et al., 2018)	Atrophic acne scars Mild to severe degree	Yes	35	Four sessions at 3-week intervals: 1) Microneedling + PRP on the left side of the face	Topical	-Microneedling, 1.5 mm deep	-Goodman and Baron qualitative -Patient satisfaction	Follow-up at 3 months -Both sides of the face showed significant improvement in scars after treatment.	Microneedling + PRP caused less erythema and edema
					2) Microneedling alone on the right side of the face				-No significant difference between the sides	
11	Deshmukh and Bel gaumkar (2018)	Atrophic acne scar Goodman score: 2, 4	Yes	40	Four sessions at 4-week intervals: 1) PRP + subcision on the right side	Intradermal	-Subcision (by 18-20-G needle is inserted at 30°)	-Goodman and Baron qualitative Patient satisfaction	Improvement was evaluated by a blinded investigator 2 months following treatments -The right side showed greater improvement (32.08%) than the left side (8.33%) ($p = 0.004$)	-Erythema, edema, and stinging occurred equally on both sides in all subjects -PIH on both sides in 17.5% of patients
					2) Subcision on the left side				-The patients' subjective score on the right side (45.28%) was significantly higher than on the left side (20.74%). ($p = 0.034$)	
12	Min et al. (2018)	Atrophic acne scar Moderate to severe	Yes	25	Two monthly sessions, 1) Fractional CO_2 laser + PRP (unilateral)	Intradermal	-Ablative fractional CO_2 laser (10,600 nm)	-Investigator's global assessment (IGA) -Echelle d'evaluation clinique des cicatrices d'acne (ECCA) scores	Follow-up at 3 months after treatment -Better results with laser + PRP based on both IGA and ECCA scoring systems.	-Erythema (less on PRP treated side) -Hyperpigmentation
					2) Fractional CO_2 laser + saline injections on the opposite side					

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
13	Ibrahim et al. (2017)	Atrophic scars due to acne, trauma, and varicella	No	90	Patients were randomized into three groups:	Intradermal	Microneedling, 0.25–2.5 mm deep	-Goodman and Baron qualitative	Follow-up at 3 months:	Higher pain score in the micro-needling single-therapy group
		Goodman score: 2–4			1) Microneedling, three sessions at 4 weeks (28patients)			-Quartile grading scale	-The highest response rate was in the combination group (micro-needling plus PRP)	More severe erythema in PRP + microneedling group
					2) PRP, six sessions at 2 weeks (34patients)				-In PRP single-therapy group, rolling scars responded better to the treatment than boxcar or icepick scars.	
					3) Microneedling + PRP, six sessions at 2 weeks (28patients)					
14	Kar and Raj (2017)	Atrophic acne scars	Yes	30	Three monthly sessions:	Topical	Fractional ablative CO_2 laser (FCL)	-Goodman and Baron qualitative	Follow-up after a month	-Erythema, edema, pain (all milder on the PRP treated side)
		Goodman score: 3–4			1) Fractional CO_2 laser on the right side of the face			-Quartile grading scale	-Both sides improved significantly compared with the baseline	
					2) Fractional CO_2 laser + PRP on the left side			-Patient satisfaction	-No significant difference in the degree of improvement between the groups.	
15	Abdel Aal et al. (2018)	Atrophic acne scars	Yes	30	Two sessions at 3–4-week intervals:	Intradermal	-Ablative CO_2 fractional laser (10,600 nm)	-Goodman and Baron qualitative	Follow-up 6 months after the last laser session:	-Faster improvement of erythema in group 2 ($p = 0.0052$)
		Mild to severe			1) Fractional CO_2 laser (left side)			-Quartile grading scale	-Better results were observed with laser + PRP.	-PIH occurred in 16.6% of the first group, especially with darker skin phototypes ($p = 0.001$)
					2) Fractional CO_2 laser + PRP (right side)			-Patient satisfaction	-Higher patients' satisfaction with laser + PRP.	-Acneiform eruption was reported in 13.3% of the first and 6.6% of the second group

(Continues)

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
16	Hodeib et al. (2018)	Striae alba on different body sites	Yes	20	Four sessions at 3-4-week intervals: 1) PRP on the right side 2) Carboxytherapy on the left side	Intradermal	-Carboxytherapy (100 ml gas with flow rate 80–150 cc/min) by A 30-G needle was injected	-Goodman and Baron qualitative -Quartile grading scale -Patient satisfaction	Follow-up after 3 months: -Both groups showed significant improvement (ranging from 20% to 80%), with the mean ± SD of 44.50 ± 18.15 for group 1 and 48.50 ± 18.45 for group 2. -No significant difference was observed between the methods. -Fibronectin-stained area was significantly higher in group 2 than in group 1 ($p < 0.001$) and significantly higher in both groups after treatment compared to the baseline	Ecchymosis and pain during injection in both groups
17	Faghihi et al. (2016)	Atrophic acne scars Moderate to severe	Yes	16	Two monthly sessions: 1) Fractional CO_2 laser + PRP (unilateral) 2) Fractional CO_2 laser + saline injection on the opposite side	Intradermal Two-stage centrifugation process	-Ablative fractional carbon dioxide laser	-Goodman and Baron qualitative -Quartile grading scale -Patient satisfaction	Follow-up at 1 month and 5 months: -There was no significant difference between the two groups.	Erythema and edema in patients treated with PRP
18	Asif et al. (2016)	Atrophic acne scars Goodman score: 2–4	Yes	50	Three monthly sessions: 1) Microneedling + PRP on the right side of the face	Intradermal	Microneedling, 1.5 mm deep	-Goodman qualitative -Goodman quantitative	Follow-up at 3 months: PRP-treated and distilled water-treated sides showed 62.20% and 45.84% improvement on the goodman quantitative scale. (p-value <0.00001)	Acne flares and bruising: 4%, Milia: 2%

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
					2) Microneedling + distilled water intradermally on the left side of the face			-Evaluation of independent dermatologist scores	-PRP-treated side indicated excellent response in 40% of the patients and good response in 60% of the patients, while the placebo group had an excellent response in just 5% of the patients. The difference was statistically significant.	Persistent erythema: 2%, PIH: 8%
19	Gawdat et al. (2014)	Atrophic acne scars Goodman score: 2–4	Yes	30	Patients were randomized into two groups, three monthly sessions: 1) Fractional CO_2 laser + PRP on one side and fractional CO_2 laser + saline on the other side (15 patients)	Intradermal Double spin method	Fractional ablative carbon dioxide laser (FCL)	-Goodman and Baron qualitative -Quartile grading scale	Follow-up after 6 and 9 months: -Patients receiving PRP experienced a better improvement in skin smoothness and OCT than those receiving normal saline. ($p = 0.03$)	-Erythema, PIH, edema, crusting, and acne eruption lasted for a shorter duration in patients receiving PRP. -Periprocedural pain was significantly greater in patients receiving intradermal PRP
					2) Fractional CO_2 laser + PRP on one side and fractional CO_2 laser + topical PRP on the other (15 patients)			-Patient satisfaction -Optical coherence tomography (OCT)	-Results were equal with topical and intradermal PRP	
20	Chawla, (2014)	Atrophic acne scar Goodman score: 2–4	Yes	30 (27 completed the study)	Four sessions at 4-week intervals: 1) Microneedling + PRP (right side) 2) Microneedling + topical vitamin C (left side)	Topical Double-spin method			-Microneedling, 1.5 mm deep	-Goodman and Baron qualitative

(Continues)

TABLE 1 (Continued)

	Study	Type of scar and goodman severity	Split face	Number of patients (N)	Intervention groups	PRP administration route	Combination treatment	Assessment index	Results	Side effects
21	Nofal et al. (2014)	Atrophic acne scar with Goodman score: 2–4	No	45	Patients were randomized into three groups, three sessions at 2-week intervals: 1) PRP (15 patients) 2) TCA 100% focal (15 patients) 3) PRP + micro-needling	Intradermal in group 1 and topical in group 3	-Micro-needling, 2 mm deep -TCA is 100% focal	-Goodman and Baron qualitative -Quartile grading scale -Patient satisfaction	Follow-up 2 weeks after the last treatment: -Highly significant improvement in all groups compared with baseline. -There was no significant difference between the groups in terms of quartile grading scale or patients' satisfaction	Periprocedural pain
22	Lee et al. (2011)	Atrophic acne scars Moderate to severe	Yes	14	Two monthly sessions: 1) Fractional CO_2 laser + PRP (one side) 2) Fractional CO_2 laser + saline injection on the opposite side	Intradermal Double spin method	Q-ray ablative fractional CO_2 laser	-Quartile grading scale	Follow-up at 5 months: -Clinical improvement was significantly greater in the PRP group compared to the saline group ($p = 0.03$)	Erythema, edema, and crusting improved faster in the PRP group ($p = 0.01$).
23	Hewedy et al. (2020)	Keloids on different body sites	No	40	Patients were randomized into two groups 1) Triamcinolone acetonide 20 mg/ml intralesional injection every 3 weeks for four sessions + PRP injection 1 week after each session (20 patients) 2) Triamcinolone acetonide 20 mg/ml intralesional injection (20 patients)	Intradermal	Triamcinolone acetonide 20 mg/ml	-Vancouver scar scale (VSS) -Verbal rating scale (VRS)	Follow-up at 3 months: -All parameters of VSS showed significant improvement in both groups ($p = 0.001$ for both) -VSS results showed significantly greater improvement in group 1 compared with group 2 ($p = 0.026$)	-Higher incidence of hypopigmentation, atrophy, and telangiectasia was observed in group 2 -After treatment, both groups showed significant improvement in pain and itching

Abbreviations: DOT, Dermal optical thermolysis; ECCA, Echelle d'evaluation clinique des cicatrices d'acne (acne scar clinical grading scale); IGA, Investigator's global assessment; PIH, Post-inflammatory hyperpigmentation; SC-CM, System Center Configuration Manager; TCA, Trichloroacetic acid; YAG, Yttrium aluminum garnet.

TABLE 2 Quality assessment of the included studies (quality of assessment checklist is available in Appendix 2)

First author	Item number in checklist																											Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
HEBA I. GAWDAT (Cervelli et al., 2011)	1	1	1	1	1	1	1	1	0	1	3	1	1	1	0	1	1	1	1	1	1	1	1	0	1	3	1	22
Ahmed Mohammed Abdel Aal (Chicharro-Alcántara et al., 2018)	1	0	1	1	1	1	1	1	0	1	3	1	1	1	1	1	1	1	1	1	1	1	1	0	1	3	0	21
Mohd Asif (Gentile et al., 2014)	1	0	1	1	1	1	1	1	1	1	3	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	0	21
Nashwa N. Elfar (Chawla, 2014)	1	1	1	1	0	1	0	1	0	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	0	3	2	22
Moetaz El-Domyati (Gentile et al., 2015)	1	1	0	1	1	1	1	1	0	1	3	1	1	1	1	1	1	1	1	1	1	1	1	0	1	3	1	22
Moustafa A. El-Taieb (De Angelis et al., 2019)	1	1	1	1	0	1	1	1	0	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	0	3	2	23
Gita Faghihi (Gentile and Garcovich, 2021b)	1	1	0	1	1	1	1	1	0	1	3	1	1	1	1	1	1	1	1	1	1	1	1	0	1	3	0	21
Ola Galal (Lynch & Bashir, 2016)	1	0	1	1	1	1	1	1	0	1	3	1	1	0	0	1	1	1	1	1	1	1	1	1	1	3	0	20
Abeer A Hodeib (Gentile & Garcovich, 2020)	1	1	1	1	1	1	1	1	0	1	3	1	1	1	3	1	1	1	1	1	1	1	1	0	1	3	0	21
Zeinab A. Ibrahim (Hassan et al., 2020)	1	1	1	1	0	1	1	1	1	1	3	1	1	0	0	1	1	1	1	1	1	1	1	0	0	1	2	22
N Agamia (Nicoli et al., 2015)	1	1	1	1	0	1	0	1	0	1	3	1	1	1	0	1	1	1	1	1	1	1	1	1	0	3	1	20
Eman Nofal (Giordano et al., 2017)	1	1	1	1	0	1	0	1	0	1	3	1	1	1	1	1	1	1	1	1	1	1	1	0	0	3	2	21
Akmal Saad Hassan (Min et al., 2018)	1	1	1	1	1	0	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	23

Twelve percent of the patients who received PRP as a single treatment for their scars showed excellent improvement, which was substantially higher than the excellent response rate with single laser therapy (zero) or micro-needling single therapy (3%). More patients in the PRP-only group showed a poor response rate (29%) than in the micro-needling (25%) or laser (16%) groups. In addition, a weak response to treatment was least frequent among those receiving PRP along with either laser or micro-needling (4% and 5%, respectively), meaning that most of these patients showed moderate and better responses.

When added to micro-needling, PRP increased the response rate for excellent improvement from 3% to 23% and for a marked improvement from 19% to 43%. Similarly, patients receiving laser for their conditions showed higher rates of excellent responses when PRP was added to their treatment combination (32% compared to none) Also, the poor results with laser and micro-needling rates were considerably higher when used alone (16% and 25%, respectively) than when combined with PRP (4% and 5%, respectively).

A moderate response to treatment was most frequently observed in the micro-needling group (46%), followed by laser (36%) and PRP (36%), PRP plus laser (24%), and PRP plus micro-needling (18%), in decreasing order of frequency.

4 | PUBLICATION BIAS

The Begg's rank correlation and Egger's linear regression tests were suggestive of publication bias and a possible small study effect (Figure 3). (Fractional laser (Begg's $p = 0.007$, Eggers's $p < 0.001$), fractional laser plus PRP (Begg's $p < 0.001$, Eggers's $p < 0.001$), micro-needling (Begg's $p = 0.152$, Eggers's $p = 0.002$), micro-needling plus PRP (Begg's $p < 0.001$, Eggers's $p < 0.001$), and PRP (Begg's $p < 0.001$, Eggers's $p < 0.001$).

5 | DISCUSSION

Finding effective treatment strategies for different types of scars has been the topic of numerous studies due to their challenges for patients and clinicians. Apart from the efficacy, the safety of the treatments, cost, and convenience are other major issues to consider when discussing various therapeutic options with patients. As none of the viable therapies are ideal, new methods are being introduced with promising but still questionable efficacies and/or safety profiles.

Platelet-rich plasma is one of the relatively newer methods and is increasingly being considered a single therapy or an adjunct to other

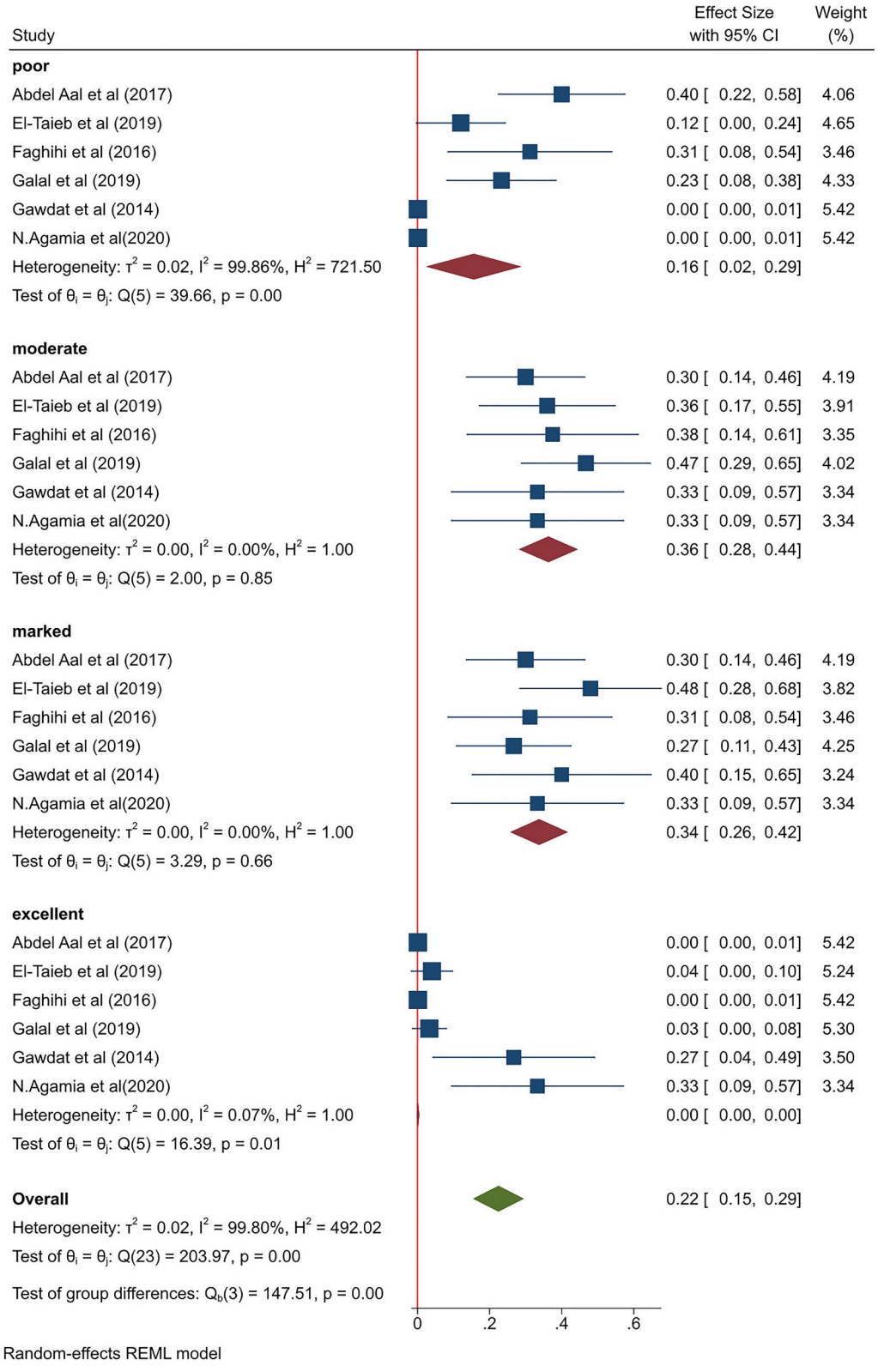


FIGURE 2 Forest plots describing the prevalence of each outcome in (a) fractional laser, (b) fractional laser with platelet-rich plasma (PRP), (c) micro-needling, (d) micro-needling with PRP, (e) PRP

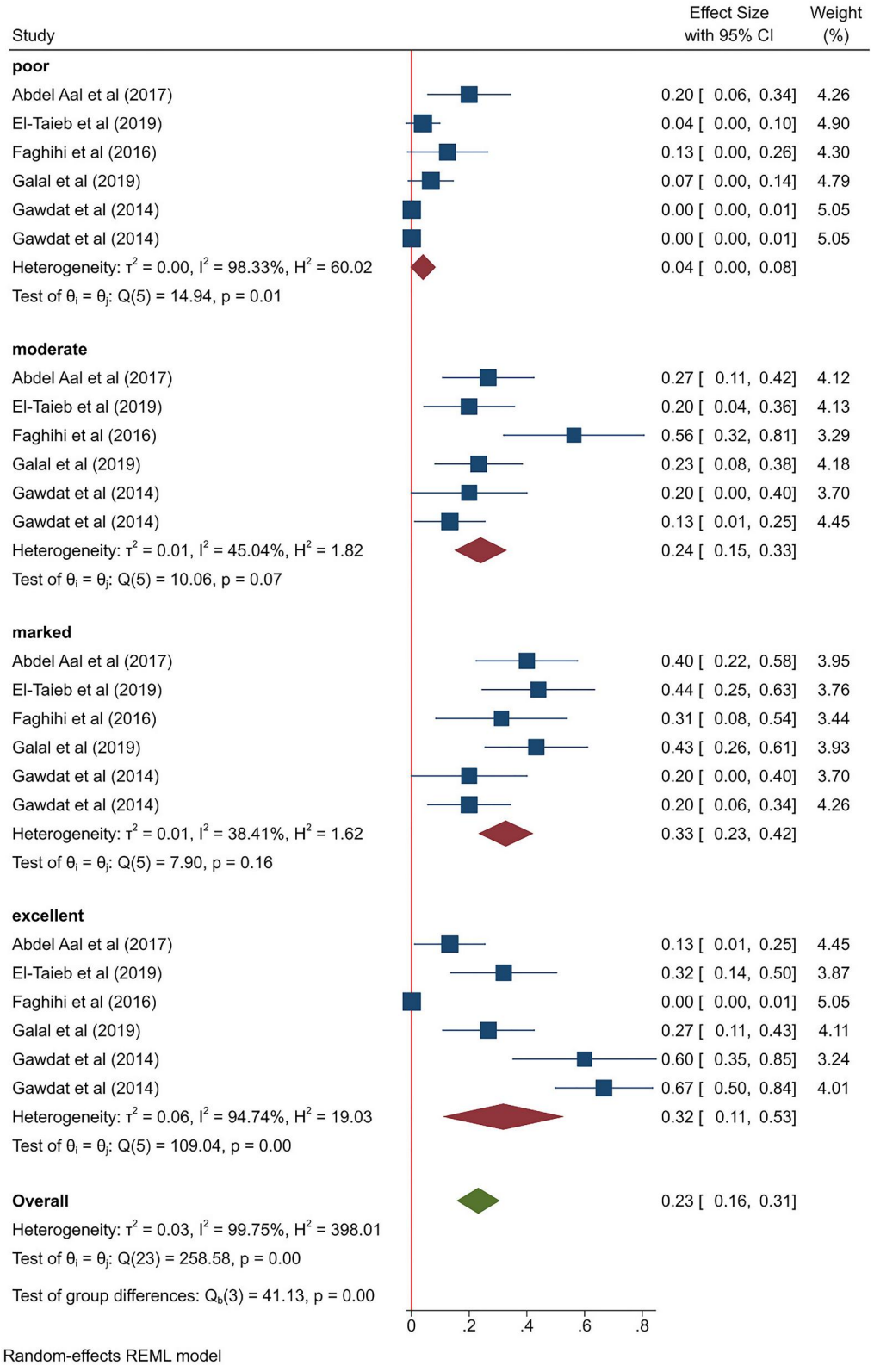
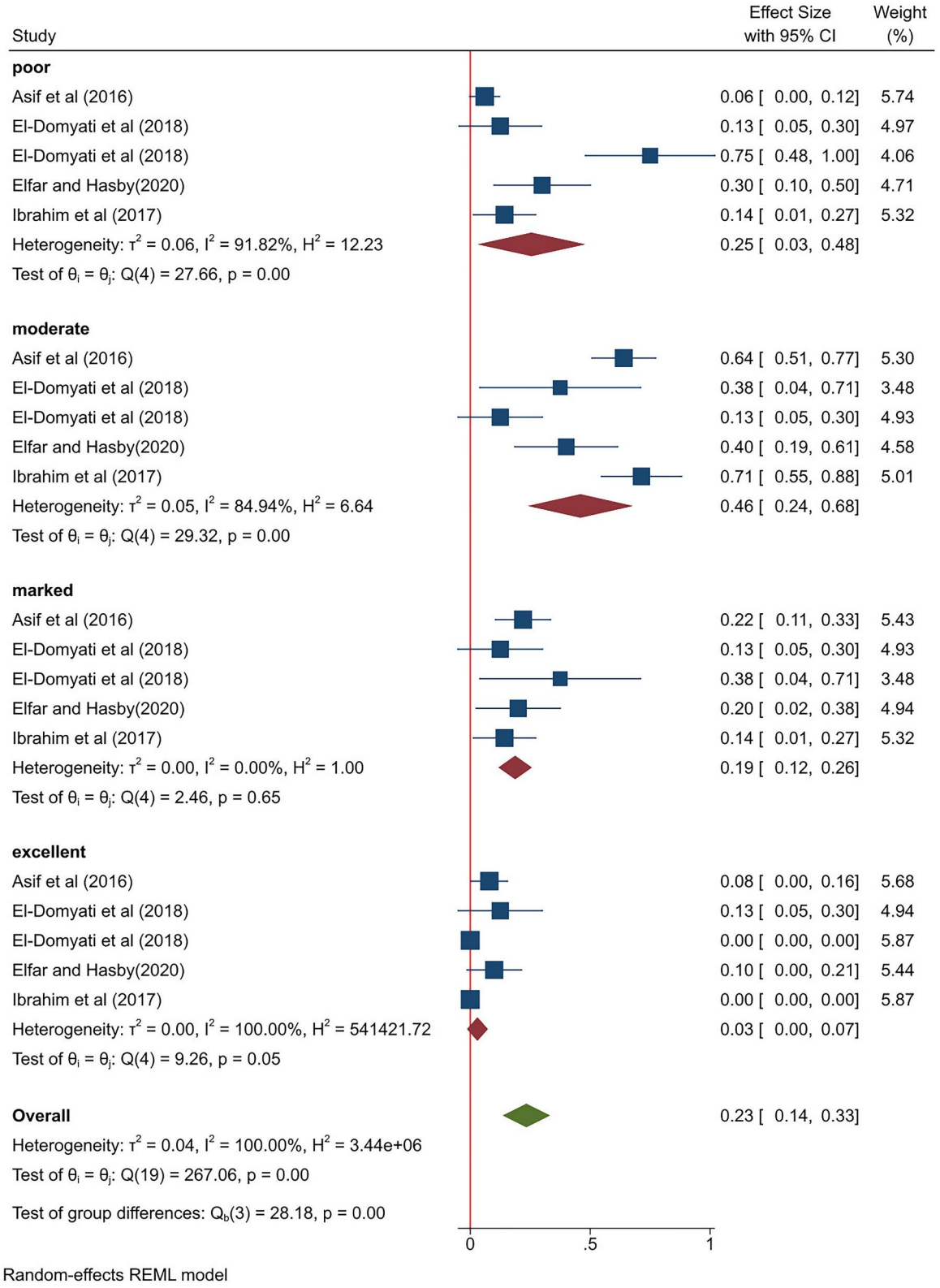


FIGURE 2 (Continued)



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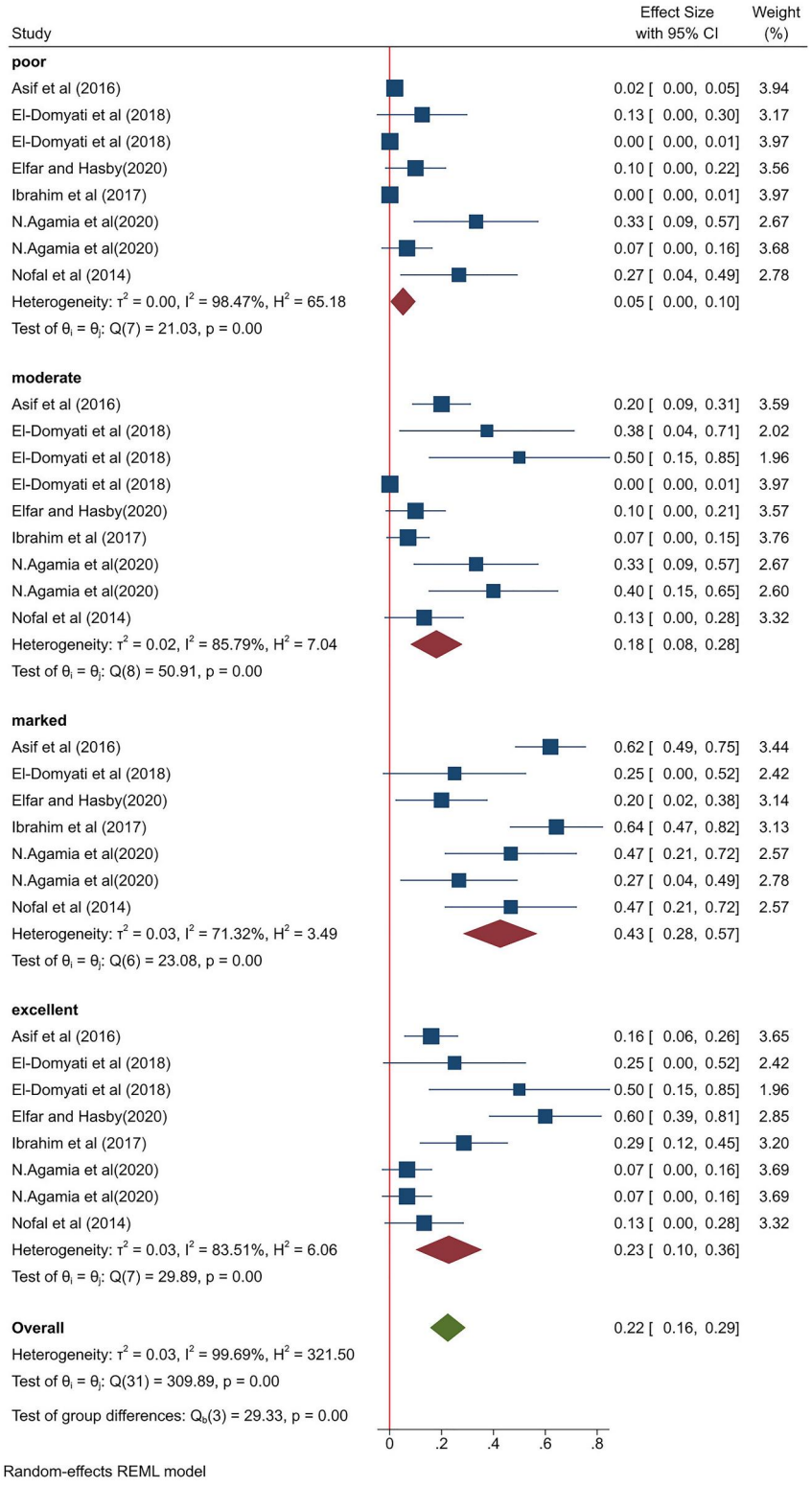


FIGURE 2 (Continued)

treatment modalities. Since its introduction in the 1970s, PRP has made its way to several fields of medicine (Alves & Grimalt, 2018). There are different types of platelet-containing products based on their fibrin and white blood cell contents that give them various properties (Alser & Goutos, 2018; Zhang et al., 2018). Pure PRP, that is, leukocyte depleted form, is the most common type used in clinical

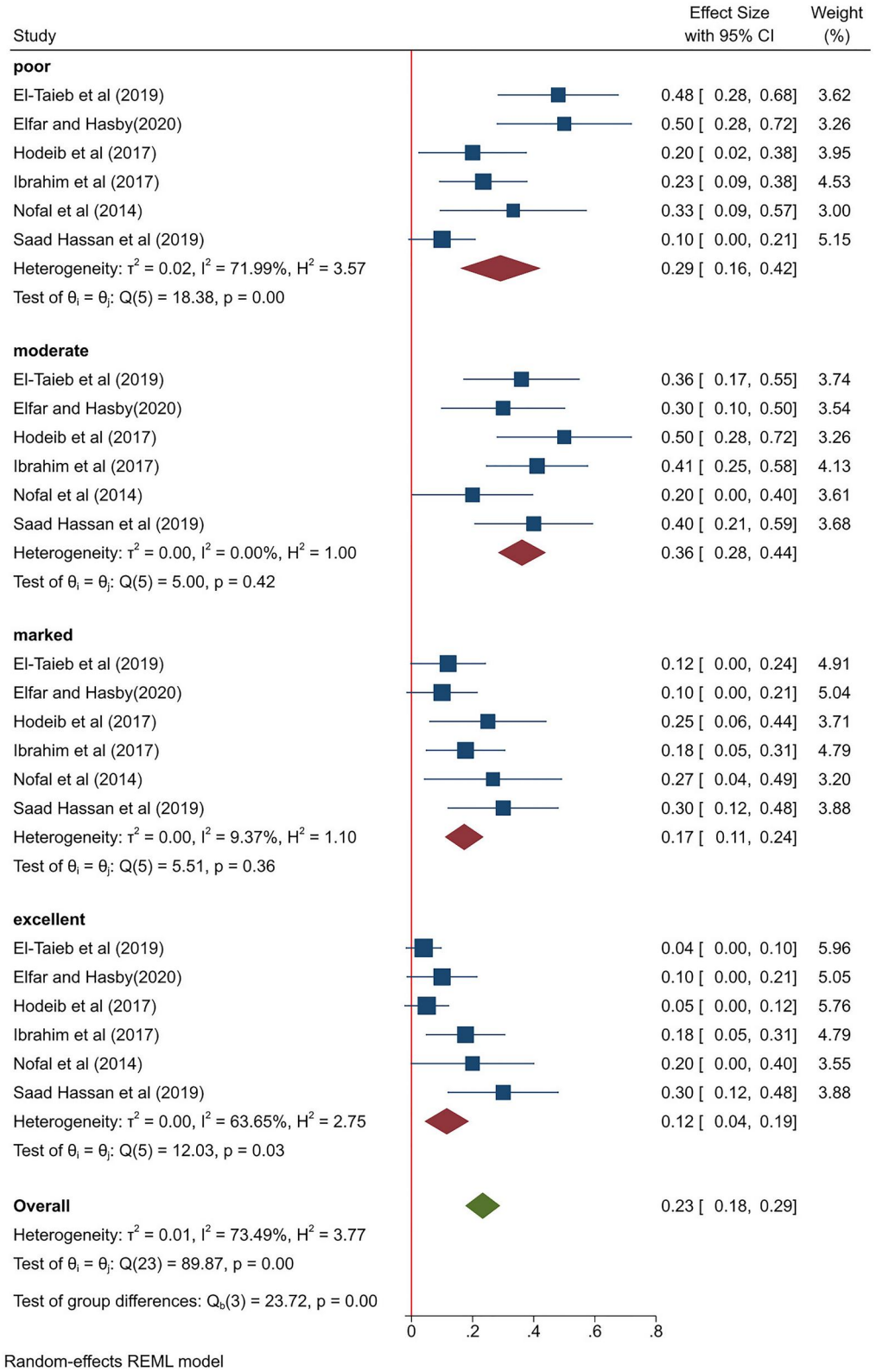


FIGURE 2 (Continued)

practice (Alser & Goutos, 2018). Platelets release various growth factors, chemokines, and bioactive molecules that affect the regenerative and inflammatory pathways in harmonious or contradictory ways. They can regulate cell migration and proliferation, ECM formation, and activities of immune cells in many ways and ultimately enhance tissue growth and repair (Andia & Abate, 2013). A review by

TABLE 3 Results of the meta-analysis, based on the type of treatment received

	PRP	PRP + microneedling	PRP + laser	Microneedling	Laser
No. of trials/arms	5/6	6/8	5/6	4/5	6
No. of patients	139	159	146	106	131
Excellent response rate	12%	23%	32%	3%	0
	95% CI: 0.04, 0.19, $I^2 = 63.65\%$	95% CI: 0.10, 0.36, $I^2 = 83.51\%$	95% CI: 0.11, 0.53, $I^2 = 94.74\%$	95% CI: 0.00, 0.07, $I^2 = 100\%$	95% CI: 0.00, 0.01, $I^2 = 0.07\%$
Marked response rate	17%	43%	33%	19%	34%
	95% CI: 0.11, 0.24, $I^2 = 9.37\%$	95% CI: 0.28, 0.57, $I^2 = 71.32\%$	95% CI: 0.11, 0.53, $I^2 = 38.41\%$	95% CI: 0.12, 0.28, $I^2 = 0.00\%$	95% CI: 0.26, 0.42, $I^2 = 0.00\%$
Moderate response rate	36%	18%	24%	46%	36%
	95% CI: 0.28, 0.44, $I^2 = 0.00\%$	95% CI: 0.08, 0.28, $I^2 = 85.79\%$	95% CI: 0.15, 0.33, $I^2 = 45.04\%$	95% CI: 0.24, 0.68, $I^2 = 84.96\%$	95% CI: 0.28, 0.44, $I^2 = 0.00\%$
Poor response rate	29%	5%	4%	25%	16%
	95% CI: 0.16, 0.42, $I^2 = 71.99\%$	95% CI: 0.00, 0.10, $I^2 = 98.47\%$	95% CI: 0.00, 0.08, $I^2 = 98.33\%$	95% CI: 0.03, 0.48, $I^2 = 91.82\%$	95% CI: 0.02, 0.29, $I^2 = 99.86\%$
Overall response rate	23%	22%	23%	23%	22%
	95% CI: 0.18,0.29	95% CI:0.16, 0.28	95% CI:0.16, 0.31	95% CI:0.14, 0.33	95% CI:0.15, 0.29
	$I^2 = 73.49\%$	$I^2 = 99.69\%$	$I^2 = 99.75\%$	$I^2 = 100\%$	$I^2 = 99.8\%$

Gentile et al. showed that PRP improved neo-angiogenesis and various fibroblastic activities, ultimately resulting in faster wound healing than hyaluronic acid, skin graft, and advanced dressings (Gentile and Garcovich, 2021a).

While being a well-recognized option in managing chronic wounds, PRP still has doubtful efficacy in other skin-related conditions (Chicharro-Alcántara et al., 2018; Lynch & Bashir, 2016). Adding PRP to Hyaluronic Acid dressing has been shown to accelerate the healing process in surgical, post-traumatic, and chronic wounds (Cervelli et al., 2011; De Angelis et al., 2019; Nicoli et al., 2015). Moreover, promising results were obtained in treating pattern alopecia with PRP alone or combined with other methods such as human follicle mesenchymal stem cell micro-grafting (Gentile et al., 2015; Gentile and Garcovich, 2020, 2021b; Giordano et al., 2017). It is worth mentioning that PRP, in conjunction with autologous fat, has shown promising results also in the management of more severe forms of scars with more prominent loss of subcutaneous tissue such as post-traumatic or burn scars, hemifacial atrophy, tissue loss due to aging, etc. (Cervelli et al., 2013; Gentile et al., 2014)

It has been a while since PRP has been used for enhancing the appearance of atrophic scars, but its application for hypertrophic/keloidal tissue is more recent and, therefore, even more controversial. This meta-analysis was designed to pool the findings of the clinical trials comparing PRP with other treatments for different types of scars. However, only studies working on atrophic scars were included in the analysis, why solely one study on hypertrophic/keloidal scars met the inclusion criteria for our review (Hewedy et al., 2020). The latter will be discussed individually. Herein we assess the results of the review based on scar categories. It must be noted that the results of the meta-analysis might have been impacted by publication bias and small study effects.

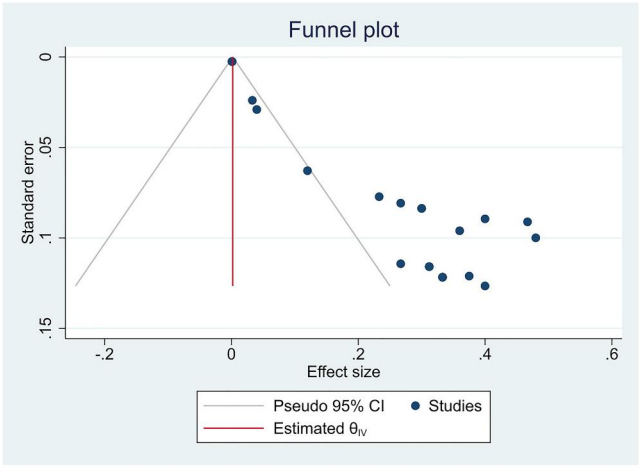
5.1 | Acne scars

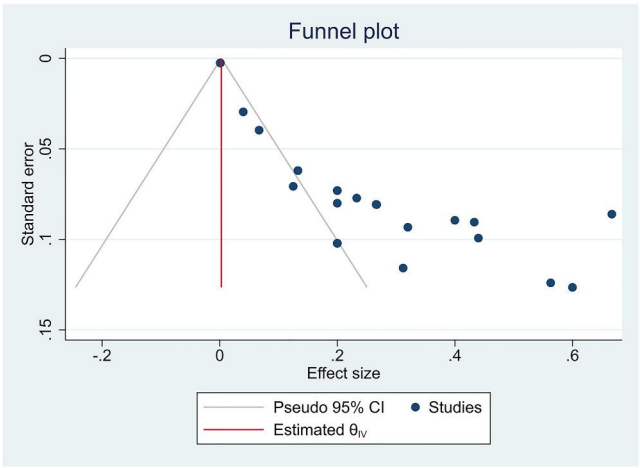
The majority of the studies in this review focused on different types of atrophic acne scars. Results of the meta-analysis suggest that PRP is an effective and safe treatment as either a single or added therapy for atrophic scars.

Overall, 23% of the patients receiving only PRP showed improvement in their scar scores, comparable to the total response rates observed with laser (22%) or micro-needling (23%). However, the degree of improvement often varied among the responders. For example, roughly twice as many patients in the laser group (34%, 45 patients) as in the PRP group (17%, 24 patients) experienced marked improvement. Also, 12% (17 patients) of patients in the PRP group and none in the laser group showed excellent responses. The poor response rate in the laser group (16%, 21 patients) was almost half of that of the PRP group (29%, 41 patients).

In each of the three single-therapy groups, that is, micro-needling, ablative lasers, or PRP, the highest percentage of patients clustered at moderate treatment response instead of the combinational regimens where most patients experienced marked or excellent improvement.

The results of our analysis show that PRP might be most helpful when combined with other more invasive treatment methods such as micro-needling or ablative lasers. It is considerable how the addition





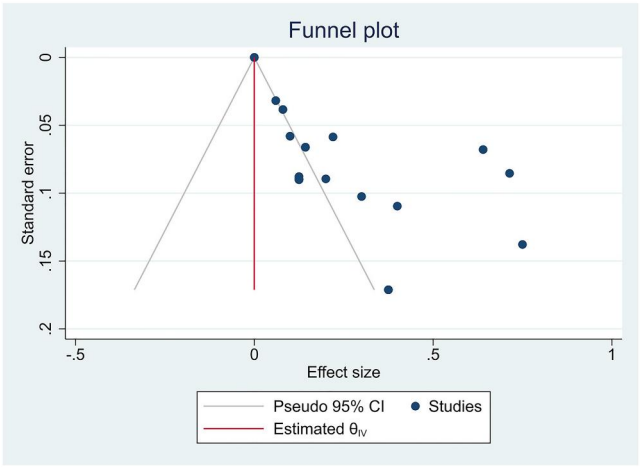
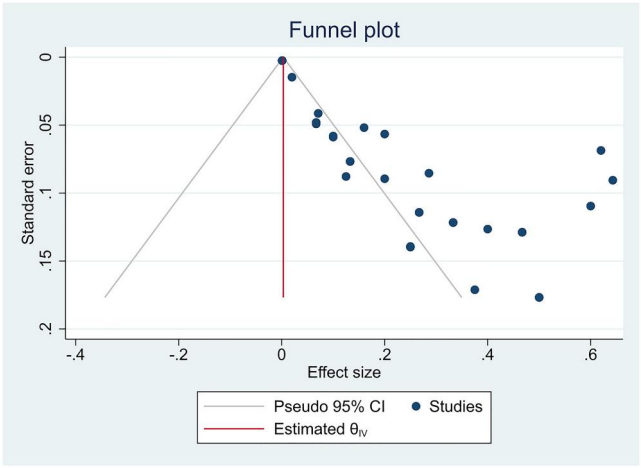


FIGURE 3 Funnel plot distribution of the studies for (a) fractional laser, (b) fractional laser with platelet-rich plasma (PRP), (c) micro-needling, (d) micro-needling with PRP, (e) PRP

of PRP to micro-needling or laser raises the rates of marked and excellent responses. Just below a third of patients treated with ablative lasers plus PRP (as opposed to 0% of those treated with laser alone), and nearly a quarter of those treated with micro-needling plus PRP (compared with 3% of the patients treated with only micro-needling) showed excellent improvement in their overall scar scores.



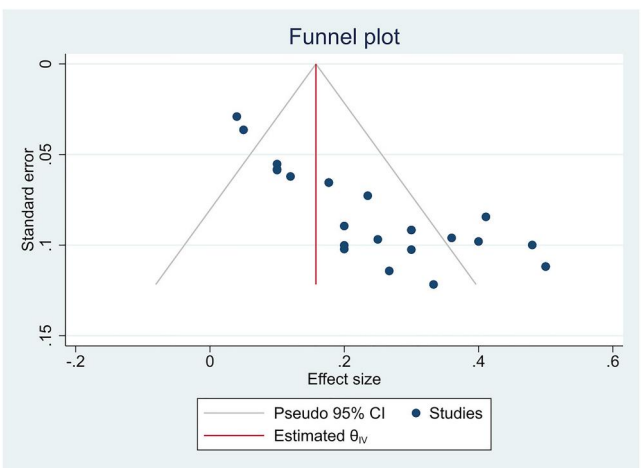


FIGURE 3 (Continued)

Another third in the laser plus PRP group experienced marked improvement. The rate was 43% for the micro-needling plus PRP group. Treatment responses with these two combinations were generally inclined toward more desirable results.

The poor response rate was highest in the PRP single-therapy group, followed by micro-needling and laser single-therapies at roughly 30%, 25%, and 16%, respectively. Whereas only one out of 25 patients receiving laser plus PRP and one out of 20 patients receiving micro-needling plus PRP experienced poor results.

Overall, the results of this meta-analysis suggest that PRP is most efficacious when administered in conjunction with other more invasive therapeutic modalities. At the same time, as a single therapy, it appears to be a less desirable option in terms of efficacy compared to the ablative lasers or micro-needling. Moreover, several studies reported fewer numbers or faster improvement of adverse reactions such as erythema, edema, crusting, pain, and post-inflammatory hyperpigmentation among the subjects receiving PRP.

Most of the reviewed studies not included in the meta-analysis supported the results in that the invasive therapies, such as micro-needling, ablative lasers, or subcision, were either more effective or less problematic in terms of side effects if combined with PRP than when used alone.

5.2 | Striae Alba

In a study comparing intradermal PRP with carboxytherapy, Hodeib et al. showed improvement in the appearance of striae and the amount of deposited fibronectin in the PRP-treated lesions.

5.3 | Trauma scars

In the study by Agamia et al., micro-needling plus PRP, when performed frequently enough, showed comparable results to ablative laser in treating traumatic atrophic scars.

5.4 | Hypertrophic/Keloid scars

Evidence supporting the role of PRP in the management of keloids is scarcer than atrophic scars. In the only two-arm clinical trial that met our inclusion criteria, Hewedy et al. reported better results and fewer side effects such as atrophy, hypopigmentation, and telangiectasia with Triamcinolone Acetonide plus PRP than with Triamcinolone Acetonide alone.

Jones ME et al. performed surgery, PRP, and radiotherapy for two series of patients with 44 and 50 keloidal scars, respectively, where recurrence was observed in 4.5% and 6%. Therefore, these studies had no control groups and were not included in our review or meta-analysis (Jones et al., 2017).

6 | STUDY LIMITATIONS

It is difficult to come to an accurate estimate of the efficacy and safety of PRP since the studies have been heterogeneous in many regards. Firstly, small variations in the PRP preparation methods, whether manual or automated, can yield products with different concentrations of platelets, white blood cells, fibrin, or platelet activators (Chicharro-Alcántara et al., 2018). Besides, most of the studies are relatively small-sized and follow the patients for a short time. Also, the studies are diverse regarding the treatment protocols, administration routes, injection sites intervals, or delivered volumes of the preparations. Different patient populations across the investigations and even within them are influential factors. Studies comparing the treatment in different skin phototypes are lacking. Besides, most authors evaluate scars with differing etiologies, types, severities, and durations without separating them. Other varying factors among the studies were related to the associated treatments. The variable settings of the ablative lasers, the types and depths of needling, or the subcision technics also play their parts in the final results. It is also worth mentioning that the assessments are, to a great part, subjective and procedures are operator-dependent.

Considering the ever-increasing acceptability of PRP, more extensive studies, including all types of scars and more accurate control of the variables, are needed to provide enough evidence to support its use.

7 | CONCLUSION

According to the results of this study, PRP appears to have a response rate roughly equal to ablative lasers and micro-needling in the treatment of atrophic scars. Furthermore, more favorable results and fewer, shorter-lasting side effects were observed in patients who responded to their treatments when PRP was added to their treatment regimens. Based on the existing data, PRP seems to be a viable adjunct to the more aggressive cutaneous interventions for treating atrophic scars owing to its ability to enhance the healing process or reduce undesirable side effects. However, caution must be exerted when interpreting the results as the studies with smaller sample sizes; thus, lower powers are generally more likely to show favorable results (small study effect), and studies with more favorable results are more likely to become published (publication bias), both of which were suggested here by the quality assessments. Also, the results of the studies were statistically inconsistent in most parts, as shown by Higgin's I^2 statistic. Whether adding PRP to the list of therapies for hypertrophic/keloidal scars is reasonable remains questionable as the evidence is far from adequate. High power studies with higher sample volumes, better classification, and control of the variables require longer follow-up periods to allow more accurate assumptions. Also, more studies on atrophic scars for reasons other than acne are needed to conclude different types of atrophic scars.

AUTHOR CONTRIBUTIONS

Zahra Ebrahimi contributed to the search process, data extraction, validation, and original draft writing. Yousef Alimohamadi contributed to the study concept and design and editing of the draft, Majid Janani contributed to data extraction, data analysis, and interpretation, and writing a draft, Mahboobeh Kamal contributed to the search process, extraction of the data, quality assessment; Pardis Hejazi participated in data extraction, and interpretation wrote the manuscript and performed the final edition, and finally, Azadeh Goodarzi was the supervisor of the study, contributed to the study concept, interpretation of the results, and critical revision of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

Abdel Aal, A. M., Ibrahim, I. M., Sami, N. A., & Abdel Kareem, I. M. (2018). Evaluation of autologous platelet-rich plasma plus ablative carbon dioxide fractional laser in the treatment of acne scars. *Journal of Cosmetic and Laser Therapy*, *20*(2), 106–113.

Abdel-Maguid, E. M., Awad, S. M., Hassan, Y. S., El-Mokhtar, M. A., El-Deek, H. E., & Mekkawy, M. M. (2019). Efficacy of stem cell-conditioned medium vs. platelet-rich plasma as an adjuvant to ablative fractional CO_2 laser resurfacing for atrophic post-acne scars: A split-face clinical trial. *Journal of Dermatological Treatment*, 1–8.

Agamia, N. F., Sorror, O., Alrashidy, M., Tawfik, A. A., & Badawi, A. (2020). Clinical and histopathological comparison of microneedling combined with platelets rich plasma versus fractional erbium-doped yttrium aluminum garnet (Er: YAG) laser 2940 nm in treatment of atrophic post traumatic scar: A randomized controlled study. *Journal of Dermatological Treatment*, 1–8.

Alser, O. H., & Goutos, I. (2018). The evidence behind the use of platelet-rich plasma (PRP) in scar management: A literature review. *Scars, burns & healing*, *4*, 2059513118808773. https://doi.org/10.1177/2059513118808773

Alves, R., & Grimalt, R. (2018). A review of platelet-rich plasma: History, biology, mechanism of action, and classification. *Skin appendage disorders*, *4*(1), 18–24.

Andia, I., & Abate, M. (2013). Platelet-rich plasma: Underlying biology and clinical correlates. *Regenerative Medicine*, *8*(5), 645–658.

Arsiwala, N. Z., Inamadar, A. C., & Adya, K. A. (2020). A comparative study to assess the efficacy of fractional carbon dioxide laser and combination of fractional carbon dioxide laser with topical autologous platelet-rich plasma in post-acne atrophic scars. *Journal of Cutaneous and Aesthetic Surgery*, *13*(1), 11.

Asif, M., Kanodia, S., & Singh, K. (2016). Combined autologous platelet-rich plasma with microneedling verses microneedling with distilled water in the treatment of atrophic acne scars: A concurrent split-face study. *Journal of Cosmetic Dermatology*, *15*(4), 434–443.

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, *50*(4), 1088–1101. https://doi.org/10.2307/2533446

Behrangi, E., Goodarzi, A., Roohaninasab, M., Sadeghzadeh-Bazargan, A., Nobari, N. N., & Ghassemi, M. (2020). A review of scar treatment related to acne and burn. *Journal of Critical Reviews*, *7*(4), 714–722.

Bhargava, S., Kroumpouzos, G., Varma, K., & Kumar, U. (2019). Combination therapy using subcision, needling, and platelet-rich plasma in the management of grade 4 atrophic acne scars: A pilot study. *Journal of Cosmetic Dermatology*, *18*(4), 1092–1097.

Bijlard, E., Kouwenberg, C. A., Timman, R., Hovius, S. E., Busschbach, J. J., & Mureau, M. A. (2017). Burden of keloid disease: A cross-sectional health-related quality of life assessment. *Acta Dermato-Venereologica*, *97*(2), 225–229.

Bran, G. M., Goessler, U. R., Hormann, K., Riedel, F., & Sadick, H. (2009). Keloids: Current concepts of pathogenesis. *International Journal of Molecular Medicine*, *24*(3), 283–293.

Brown, J., & Bayat, A. (2009). Genetic susceptibility to raised dermal scarring. *British Journal of Dermatology*, *161*(1), 8–18.

Cervelli, V., Bocchini, I. P., Di Pasquali, C., De Angelis, B., Cervelli, G., Curcio, C. B., Orlandi, A., Scioli, M. G., Tati, E., Delogu, P., & Gentile, P. (2013). PRL platelet rich lipotransfert: Our experience and current state of art in the combined use of fat and PRP. *BioMed Research International*, *1*, 2013–2019. https://doi.org/10.1155/2013/434191

Cervelli, V., Lucarini, L., Spallone, D., Palla, L., Colicchia, G. M., Gentile, P., & De Angelis, B. (2011). Use of platelet-rich plasma and hyaluronic acid in the loss of substance with bone exposure. *Advances in Skin & Wound Care*, *24*(4), 176–181.

Chawla, S. (2014). Split face comparative study of microneedling with PRP versus microneedling with vitamin C in treating atrophic post acne scars. *Journal of Cutaneous and Aesthetic Surgery*, *7*(4), 209–212.

Chicharro-Alcántara, D., Rubio-Zaragoza, M., Damiá-Giménez, E., Carrillo-Poveda, J. M., Cuervo-Serrato, B., Peláez-Gorrea, P., & Sopena-Juncosa, J. J. (2018). Platelet rich plasma: New insights for cutaneous wound healing management. *Journal of Functional Biomaterials*, *9*(1), 10. https://doi.org/10.3390/jfb9010010

De Angelis, B., D'Autilio, M. F., Orlandi, F., Pepe, G., Garcovich, S., Scioli, M. G., Orlandi, A., Cervelli, V., & Gentile, P. (2019). Wound healing: In vitro and in vivo evaluation of a bio-functionalized scaffold based on hyaluronic acid and platelet-rich plasma in chronic ulcers. *Journal of Clinical Medicine*, *8*(9), 1486. https://doi.org/10.3390/jcm8091486

Deshmukh, N. S., & Belgaumkar, V. A. (2019). Platelet-rich plasma augments subcision in atrophic acne scars: A split-face comparative study. *Dermatologic Surgery*, *45*(1), 90–98.

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for assessing the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology & Community Health*, *52*(6), 377–384.

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*(7109), 629–634.

El-Domyati, M., Abdel-Wahab, H., & Hossam, A. (2018). Microneedling combined with platelet-rich plasma or trichloroacetic acid peeling for management of acne scarring: A split-face clinical and histologic comparison. *Journal of Cosmetic Dermatology*, *17*(1), 73–83.

Elfar, N. N., & Hasby, E. A. (2020). Efficacy and safety of plasma gel as a new modality in treatment of atrophic acne scars. *International Journal of Dermatology*, *59*(5), 620–626.

El-Taieb, M. A., Ibrahim, H. M., Hegazy, E. M., Ibrahim, A. K., Gamal, A. M., & Nada, E. A. (2019). Fractional erbium-YAG laser and platelet-rich plasma as single or combined treatment for atrophic acne scars: A randomized clinical trial. *Dermatologic Therapy*, *9*(4), 707–717.

Fabbrocini, G., Annunziata, M. C., D'arco, V., De Vita, V., Lodi, G., Mauriello, M. C., Pastore, F., & Monfrecola, G. (2010). Acne scars: Pathogenesis, classification and treatment. *Dermatology Research and Practice*, *2010*, 893080. https://doi.org/10.1155/2010/893080

Faghihi, G., Keyvan, S., Asilian, A., Nouraei, S., Behfar, S., & Nilforoushzadeh, M. A. (2016). Efficacy of autologous platelet-rich plasma combined with fractional ablative carbon dioxide resurfacing laser in treatment of facial atrophic acne scars: A split-face randomized clinical trial. *Indian Journal of Dermatology Venereology and Leprology*, *82*(2), 162–168.

Galal, O., Tawfik, A. A., Abdalla, N., & Soliman, M. (2019). Fractional CO_2 laser versus combined platelet-rich plasma and fractional CO_2 laser in treatment of acne scars: Image analysis system evaluation. *Journal of Cosmetic Dermatology*, *18*(6), 1665–1671.

Gawdat, H. I., Hegazy, R. A., Fawzy, M. M., & Fathy, M. (2014). Autologous platelet rich plasma: Topical versus intradermal after fractional ablative carbon dioxide laser treatment of atrophic acne scars. *Dermatologic Surgery*, *40*(2), 152–161.

Gentile, P., De Angelis, B., Pasin, M., Cervelli, G., Curcio, C. B., Floris, M., Di Pasquali, C., Bocchini, I., Balzani, A., Nicoli, F., Insalaco, C., Tati, E., Lucarini, L., Palla, L., Pascali, M., De Logu, P., Di Segni, C., Bottini, D. J., & Cervelli, V. (2014). Adipose-derived stromal vascular fraction cells and platelet-rich plasma: Basic and clinical evaluation for cell-based therapies in patients with scars on the face. *Journal of Craniofacial Surgery*, *25*(1), 267–272.

Gentile, P., & Garcovich, S. (2020). Systematic review of platelet-rich plasma use in androgenetic alopecia compared with Minoxidil®, Finasteride®, and adult stem cell-based therapy. *International Journal of Molecular Sciences*, *21*(8), 2702. https://doi.org/10.3390/ijms21082702

Gentile, P., & Garcovich, S. (2021). Systematic review: Adipose-derived mesenchymal stem cells, platelet-rich plasma and biomaterials as new regenerative strategies in chronic skin wounds and soft tissue defects. *International Journal of Molecular Sciences*, *22*(4), 1538. https://doi.org/10.3390/ijms22041538

Gentile, P., & Garcovich, S. (2021). Systematic review: The platelet-rich plasma use in female androgenetic alopecia as effective autologous treatment of regenerative plastic surgery. *Journal of Plastic, Reconstructive & Aesthetic Surgery*, *75*(2), 850–859. https://doi.org/10.1016/j.bjps.2021.11.004

Gentile, P., Garcovich, S., Bielli, A., Scioli, M. G., Orlandi, A., & Cervelli, V. (2015). The effect of platelet-rich plasma in hair regrowth: A randomized placebo-controlled trial. *Stem Cells Translational Medicine*, *4*(11), 1317–1323.

Giordano, S., Romeo, M., & Lankinen, P. (2017). Platelet-rich plasma for androgenetic alopecia: Does it work? Evidence from meta analysis. *Journal of Cosmetic Dermatology*, *16*(3), 374–381.

Golnaz, M., Mahrokh, F., Azadeh, G., Siamak Farokh, F., Masoomeh, R., Mohammadreza, G, Sadeghi, S., & Behranghi, E. (2019). Comparison of the therapeutic effect of microneedling with carbon dioxide laser in hypertrophic burn scars: A randomized clinical trial. *Iranian Journal of Dermatology*, *22*(2), 53–57.

Goodarzi, A., Behrangi, E., Ghassemi, M., Nobari, N. N., Sadeghzadeh-Bazargan, A., & Roohaninasab, M. (2020). Acne scar; a review of classification and treatment. *Journal of Critical Reviews*, *7*(5), 815–823.

Goodman, G. J. (2000). Post acne scarring: A review of its pathophysiology and treatment. *Dermatologic Surgery*, *26*(9), 857–871.

Hassan, A. S., El-Hawary, M. S., Abdel Raheem, H. M., Abdallah, S. H., & El-Komy, M. M. (2020). Treatment of atrophic acne scars using autologous platelet-rich plasma vs combined subcision and autologous platelet-rich plasma: A split-face comparative study. *Journal of Cosmetic Dermatology*, *19*(2), 456–461.

Hewedy, E.-S. S., Sabaa, B. E.-S. I., Mohamed, W. S., & Hegab, D. S. (2020). Combined intralesional triamcinolone acetonide and platelet rich plasma versus intralesional triamcinolone acetonide alone in treatment of keloids. *Journal of Dermatological Treatment*, 1–7. https://doi.org/10.1080/09546634.2020.1730742

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, *327*(7414), 557–560.

Hodeib, A. A., Hassan, G. F. R., Ragab, M. N. M., & Hasby, E. A. (2018). Clinical and immunohistochemical comparative study of the efficacy of carboxytherapy vs platelet-rich plasma in treatment of stretch marks. *Journal of Cosmetic Dermatology*, *17*(6), 1008–1015.

Hootman, J. M., Driban, J. B., Sitler, M. R., Harris, K. P., & Cattano, N. M. (2011). Reliability and validity of three quality rating instruments for systematic reviews of observational studies. *Research Synthesis Methods*, *2*(2), 110–118.

Ibrahim, M. K., Ibrahim, S. M., & Salem, A. M. (2018). Skin microneedling plus platelet-rich plasma versus skin microneedling alone in the treatment of atrophic post acne scars: A split-face comparative study. *Journal of Dermatological Treatment*, *29*(3), 281–286.

Ibrahim, Z. A., El-Ashmawy, A. A., & Shora, O. A. (2017). Therapeutic effect of microneedling and autologous platelet-rich plasma in the treatment of atrophic scars: A randomized study. *Journal of Cosmetic Dermatology*, *16*(3), 388–399.

Jones, M. E., McLane, J., Adenegan, R., Lee, J., & Ganzer, C. A. (2017). Advancing keloid treatment: A novel multimodal approach to ear keloids. *Dermatologic Surgery*, *43*(9), 1164–1169.

Kar, B. R., & Raj, C. (2017). Fractional CO_2 laser vs fractional CO_2 with topical platelet-rich plasma in the treatment of acne scars: A split-face comparison trial. *Journal of Cutaneous and Aesthetic Surgery*, *10*(3), 136–144.

Lee, J. W., Kim, B. J., Kim, M. N., & Mun, S. K. (2011). The efficacy of autologous platelet rich plasma combined with ablative carbon dioxide fractional resurfacing for acne scars: A simultaneous split-face trial. *Dermatologic Surgery*, *37*(7), 931–938.

Lynch, M. D., & Bashir, S. (2016). Applications of platelet-rich plasma in dermatology: A critical appraisal of the literature. *Journal of Dermatological Treatment*, *27*(3), 285–289.

Min, S., Yoon, J. Y., Park, S. Y., Moon, J., Kwon, H. H., & Suh, D. H. (2018). Combination of platelet rich plasma in fractional carbon dioxide laser treatment increased clinical efficacy of for acne scar by enhancement of collagen production and modulation of laser-induced inflammation. *Lasers in Surgery and Medicine*, *50*(4), 302–310.

Nicoli, F., Balzani, A., Lazzeri, D., Gentile, P., Chilgar, R. M., Di Pasquali, C., Nicoli, M., Bocchini, I., Agovino, A., & Cervelli, V. (2015). Severe hidradenitis suppurativa treatment using platelet-rich plasma gel and Hyalomatrix. *International Wound Journal*, *12*(3), 338–343.

Nofal, E., Helmy, A., Nofal, A., Alakad, R., & Nasr, M. (2014). Platelet-rich plasma versus CROSS technique with 100% trichloroacetic acid versus combined skin needling and platelet rich plasma in the treatment of atrophic acne scars: A comparative study. *Dermatologic Surgery*, *40*(8), 864–873.

Seirafianpour, F., Sodagar, S., Mozafarpoor, S., Baradaran, H. R., Panahi, P., Hassanlouei, B., & Goodarzi, A. (2021). Systematic review of single and combined treatments for different types of striae: A comparison of striae treatments. *Journal of the European Academy of Dermatology and Venereology*, *35*(11), 2185–2198. https://doi.org/10.1111/jdv.17374

Shih, B., & Bayat, A. (2010). Genetics of keloid scarring. *Archives of Dermatological Research*, *302*(5), 319–339.

Sidgwick, G., & Bayat, A. (2012). Extracellular matrix molecules implicated in hypertrophic and keloid scarring. *Journal of the European Academy of Dermatology and Venereology*, *26*(2), 141–152.

Tan, J., Beissert, S., Cook-Bolden, F., Chavda, R., Harper, J., Hebert, A., Lain, E., Layton, A., Rocha, M., Weiss, J., & Dréno, B. (2022). Evaluation of psychological well-being and social impact of atrophic acne scarring: A multinational, mixed-methods study. *JAAD International*, *6*, 43–50. https://doi.org/10.1016/j.jdin.2021.11.006

Zhang, M., Park, G., Zhou, B., & Luo, D. (2018). Applications and efficacy of platelet-rich plasma in dermatology: A clinical review. *Journal of Cosmetic Dermatology*, *17*(5), 660–665.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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