META-ANALYSIS

Microneedling with Topical Insulin versus Microneedling with Platelet-Rich Plasma for Post-Acne Scars: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

Running Title: Microneedling with Insulin vs. PRP for Acne Scars.

AUTHORS:

Ebraheem Albazee [*1,2], Abdullah AlOtaibi [3], Husain Alsaffar [4], Fanr F Alraqum [5], Shouq Alkhatlan [6], Bader N Almutawaa [7], Hasan M Aziz [8].

AFFILIATIONS:

[1] Otorhinolaryngology-Head and Neck Surgery, Kuwait Institute for Medical Specializations (KIMS), Kuwait City, Kuwait.

[2] Department of Otolaryngology-Head and Neck Surgery, Al-Jahra Hospital, Al-Jahra, Kuwait.

[3] Royal College of Surgeons in Ireland (RCSI), Dublin, Ireland.

[4] Faculty of Medicine, University of Lancashire, Preston, United Kingdom.

[5] Kuwait Institute for Medical Specializations (KIMS), Kuwait City, Kuwait.

[6] Department of General Surgery, Sheikh Jaber Al-Ahmad Al-Sabah Hospital, Ministry of Health, Kuwait.

[7] Department of General Surgery, Al-Amiri Hospital, Ministry of Health, Kuwait.

[8] Albabtain Centre for Burns and Plastic Surgery, Alsabah Medical City, Ministry of Health, Kuwait City, Kuwait.

***Corresponding Author:**

Ebraheem Albazee, MD

Otorhinolaryngology-Head and Neck Surgery, Kuwait Institute for Medical Specializations (KIMS), Kuwait City, Kuwait, and a clinical researcher (GCSRT- program), Harvard Medical School, Boston, The United State. Email: Ebraheemalbazee@gmail.com, ORCID: https://orcid.org/0000-0003-1244-7769, Mobile: +96550958282.

STATEMENTS AND DECLARATIONS

Author contributions:

- Ebraheem Albazee: contributed to study conception, study design, data collection, data analysis, write up of original draft of manuscript, and review of manuscript for editorial and intellectual contents.
- Abdullah AlOtaibi: contributed to literature review, study conception, data collection, and review of manuscript for editorial and intellectual contents.
- Husain Alsaffar: contributed to literature review, study conception, data collection, and review of manuscript for editorial and intellectual contents.
- Fanr F Alraqum: contributed to literature review, study conception, data collection, and review of manuscript for editorial and intellectual contents.
- Shouq Alkhatlan: contributed to literature review, study conception, data collection, and review of manuscript for editorial and intellectual contents.
- Bader N Almutawaa: contributed to literature review, respond to the peer-reviewers, revise the manuscript, and review of manuscript for editorial and intellectual contents.
- Hasan M Aziz: contributed to supervision, and review of manuscript for editorial and intellectual contents.

All authors read and approved the final draft of manuscript.

Funding: None.

Conflict of interest: None to declare.

Ethical approval: Not applicable.

Research involving human participants and/or animals: Not applicable.

Informed consent: Not applicable.

Data transparency: All data are available within the manuscript and can be obtained from the corresponding author upon a reasonable request.

Acknowledgments: None.

PROSPERO registration: ID [CRD420261309180].

META-ANALYSIS

Microneedling with Topical Insulin versus Microneedling with Platelet-Rich Plasma for Post-Acne Scars: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

Running Title: Microneedling with Insulin or PRP for Acne Scars.

ABSTRACT

Background: Atrophic acne scarring is a prevalent and psychologically distressing sequela of acne vulgaris, often resulting from insufficient matrix remodeling and collagen loss. While microneedling is a safe treatment, its efficacy as a monotherapy is often limited. Autologous platelet-rich plasma (PRP) is the current gold standard adjuvant, but its high cost and invasiveness restrict its use. Topical insulin has emerged as a cost-effective, non-invasive alternative to promote wound healing.

Methods: A comprehensive search was conducted across PubMed, Web of Science, CENTRAL, Scopus, and Google Scholar for comparative studies published up to January 2026. Risk of bias was assessed using the RoB-2 and ROBINS-I tools. The primary outcome was significant clinical improvement (>50%). Secondary outcomes included changes in scar severity scores and adverse events. Risk ratios (RRs) and standardized mean differences (SMDs) were pooled with 95% confidence intervals (CIs). Trial sequential analysis was also performed.

Results: Five studies involving 256 patients were included. Microneedling with topical insulin was associated with a significantly higher rate of significant clinical improvement compared to PRP (RR = 1.96, 95% CI [1.30–2.95], $p < 0.0001$). However, the pooled analysis of changes in scar severity scores showed no significant difference between groups (SMD = -0.52, 95% CI [-1.44, 0.39], $p = 0.26$), with high heterogeneity. Regarding safety, there was no significant difference in the risk of post-inflammatory hyperpigmentation (RR = 0.72, 95% CI [0.14–3.62], $p = 0.69$), and no episodes of hypoglycemia were reported.

Conclusion: Microneedling with topical insulin may achieve a higher rate of significant clinical improvement than PRP, with a comparable safety profile. However, given the inconclusive trial sequential analysis, high heterogeneity, and low overall certainty of evidence, these findings should be interpreted with caution. Further adequately powered trials are required to confirm this preliminary signal.

Keywords: acne; insulin; meta-analysis; microneedling; PRP; platelet-rich plasma; scar.

Level of Evidence: Not applicable.

INTRODUCTION

Acne vulgaris, a common chronic inflammatory condition of the pilosebaceous unit, affects approximately 9.4% of the global population [1]. While the active phase of the disease is often transient, it commonly leads to permanent atrophic scarring, particularly in adolescent and young adult populations with a history of severe nodulocystic inflammation [2]. Atrophic scarring results from a distorted wound healing process, marked by insufficient matrix remodeling and the loss of dermal collagen [3]. This process has been reported to cause an imbalance in collagen subtypes, especially a higher proportion of fibrotic type-I collagen than the regenerative type-III collagen characteristic of healthy dermis [4, 5]. In addition to physical disfigurement, acne scarring is linked to significant psychological distress, including anxiety, depression, and social impairment, thereby requiring effective therapeutic interventions [6].

Standard skin renewal techniques, including fractional laser treatment and aggressive chemical peels, function by removing the outer layer of skin to encourage the reconstruction of the dermis [7]. Despite their effectiveness, these techniques carry significant risks of long-term erythema and post-inflammatory hyperpigmentation (PIH), especially among patients with Fitzpatrick skin types IV–VI [8, 9]. Accordingly, microneedling has emerged as a safer alternative. This method involves using fine needles to produce deliberate micro-injuries, which break down scar tissue, encourage the release of growth factors from platelets, and foster the new collagen synthesis without breaking the outer skin barrier [10]. However, microneedling monotherapy often yields gradual or modest results [11]. Hence, it is usually used with topical adjuvants to improve patient results by leveraging the micro-channels created by the needles for transdermal drug delivery [10].

Autologous Platelet-Rich Plasma (PRP) is widely used and established as an adjuvant for microneedling [12]. PRP is an autologous concentration of platelets that yields supraphysiological levels of bioactive proteins, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β). These components collectively promote fibroblast proliferation and collagen synthesis [12–15]. While the efficacy of PRP is widely recognized, its widespread use is constrained by high cost, the invasive venipuncture process, and

the need for dedicated centrifuges [16]. Therefore, topical insulin has recently been proposed as a cost-effective, non-invasive alternative [17]. Insulin exhibits structural resemblance to insulin-like growth factor-1 (IGF-1) and facilitates wound healing through the phosphatidylinositol 3-kinase signaling pathway [18]. This activation upregulates VEGF expression and normalizes collagen architecture.

The comparative efficacy of these two options remains controversial. While early split-face non-randomized studies (NRS) suggested that topical insulin might offer superior efficacy and cost-effectiveness [19, 20], subsequent randomized controlled trials (RCTs) have reported conflicting results, with some recent data favoring PRP for patient satisfaction and scar reduction [21–23]. Hence, this systematic review and meta-analysis aims to evaluate the efficacy and safety of microneedling with topical insulin versus microneedling with autologous PRP for the treatment of atrophic post-acne scars.

METHODS AND MATERIALS

Review Protocol and Reporting Style

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) [ID: CRD420261309180]. The study design and reporting adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24] and the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions [25]. Ethical approval was not required for this meta-analysis because it relied exclusively on previously published, publicly available studies.

Information Sources and Search Strategy

On 17th January 2026, a systematic literature search was performed across five major electronic databases: PubMed, Web of Science (WoS), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Google Scholar. The search strategy combined keywords related to the intervention and the condition: “("acne vulgaris" OR "cicatrix" OR “acne” OR "post-acne" OR

“postacne” OR "atrophic scar*" OR "acne scar*" OR "rolling scar*" OR "boxcar scar*" OR "ice pick scar*") AND (“microneedling” OR "micro-needling" OR “dermaroller” OR "skin needling" OR "percutaneous collagen induction" OR "collagen induction therapy" OR “PCI”) AND ("Insulin") AND ("platelet-rich plasma" OR "platelet rich plasma" OR “PRP” OR "platelet concentrate"). **Table S1** provides the detailed search strings and output for each database. To enhance the completeness of the systematic search, the reference lists of all included studies were manually reviewed, and trial registries (i.e., ClinicalTrials.gov, ICTRP) were searched. Additional sources (i.e., ResearchGate, medRxiv) were also examined to identify potentially eligible unpublished studies. When required, corresponding authors were contacted to obtain missing information or to clarify study details. No restrictions were imposed regarding language, country of origin, or publication status.

Eligibility Criteria

We included prospective studies, encompassing both parallel-group RCTs and split-face comparative designs, based on the following PICO framework:

- **Population (P):** adult patients with post-acne atrophic scars (ice-pick, boxcar, or rolling), regardless of skin type (Fitzpatrick I-VI).
- **Intervention (I):** microneedling combined with topical insulin application.
- **Control (C):** microneedling combined with PRP application.
- **Outcomes (O): primary outcomes:** significant clinical improvement in scar severity defined as at least > 50% improvement assessed via standardized scales, such as the Goodman & Baron quantitative/qualitative scale or acne scar assessment scale (ASAS). **Secondary outcomes:** change in scar severity scale, patient satisfaction score, and the incidence of adverse events (including pain, erythema, edema, and post-inflammatory hyperpigmentation).

Study Selection Process

Records were managed and screened using an electronic platform. Two investigators independently screened studies in a two-stage process, beginning with title and abstract screening, followed by full-

text assessment of potentially eligible articles. Disagreements were resolved through consensus. The same approach was applied during the risk of bias assessment and statistical analysis.

Data Extraction

A standardized Excel extraction form was developed and pilot-tested using a subset of eligible studies. The form captured data in three categories: (1) Study characteristics: study design (parallel vs. split-face), country, sample size, insulin protocol (dosage/concentration), PRP protocol (preparation method), microneedling protocol (device type and needle depth), treatment schedule, and follow-up duration; (2) Baseline demographics: age, gender, Fitzpatrick skin type, scar type distribution, and baseline scar severity scores; and (3) Outcome data: as mentioned above.

Data extraction was performed independently by at least two reviewers. The first author (EA) resolved discrepancies. For the primary dichotomous outcome (significant clinical improvement >50%), data were extracted as the number of responders exactly as categorized and reported by the original study investigators. We did not perform any continuous-to-binary data conversions. For continuous variables, to account for baseline imbalances across groups, we extracted the mean change from baseline (post-treatment minus pre-treatment scores) and their associated standard deviations.

Risk of Bias and Certainty of Evidence

At least two reviewers independently assessed the risk of bias for each included RCT. For parallel-group RCTs, we used the standard Cochrane Risk of Bias 2 (RoB-2) tool for individually randomized trials [26]. For split-face NRS, we used the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [27], evaluating bias across seven domains: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result.

Additionally, the overall certainty of the evidence was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [28, 29], which

considers limitations such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. All judgments were justified and documented, with disagreements resolved through a consensus-based process.

Effect Measures and Meta-Analysis

All statistical analyses were performed using Stata/SE software, version 19 (StataCorp). Dichotomous outcomes were analyzed using risk ratios (RR). Given the variability in the clinical scar assessment tools across the included trials, continuous outcomes were pooled using standardized mean differences (SMDs). We calculated 95% confidence intervals (CIs) for all estimates. For zero-cell values, a continuity correction of 0.5 was applied. A p-value < 0.05 was considered statistically significant. We employed a random-effects model (REML) in the primary analysis to account for observed heterogeneity in scar type and treatment protocols. Heterogeneity was assessed using the Chi-squared test and the I^2 statistic. To evaluate the robustness of the pooled estimates, a leave-one-out sensitivity analysis was performed, systematically removing each study to determine its influence on the overall effect size. Also, we conducted a predefined subgroup analysis based on the study design (parallel-group RCTs versus split-face comparative studies). Finally, publication bias could not be evaluated as we included fewer than 10 studies [30].

Trial Sequential Analysis

To assess the robustness of the findings and control for Type I and Type II errors, Trial Sequential Analysis (TSA) was conducted using the TSA software [31], examining the cumulative Z-curve against the monitoring boundaries. The Required Information Size (RIS) was calculated based on an overall two-sided Type I error (alpha) of 5%, a statistical power of 80%, and a control event rate of 18.0%. To avoid subjective assumptions regarding the anticipated intervention effect, we utilized the software's empirical estimate. We used an O'Brien-Fleming alpha-spending function to construct the monitoring boundaries, and the cumulative Z-curve was examined against them to determine whether the evidence was conclusive.

RESULTS

Search Results and Study Selection

A total of 123 records were retrieved from the initial literature search across five databases. After removing 17 duplicates, the remaining 106 articles were screened. Consequently, 93 studies were excluded for failing to meet the inclusion criteria. Thirteen articles were sought, of which one was not retrieved. Twelve studies were evaluated for eligibility by screening their full texts. Seven studies were excluded for various reasons **(Table S2)**. Finally, five studies were included in the review [19–23] **(Figure 1)**.

Characteristics of Included Studies

Five studies (three parallel-group RCTs and two split-face NRS), involving a total of 256 patients, were included in our analysis [19–23]. The three parallel-group RCTs enrolled 190 patients, while the two split-face NRS enrolled 66 patients. A key characteristic of the included cohorts was variation in skin phenotypes, with multiple studies specifically targeting Fitzpatrick skin types III-VI to assess safety and the risk of dyspigmentation. Detailed study designs and baseline patient data are summarized in **(Tables 1 and 2)**, respectively.

Risk of Bias and Certainty of Evidence

The parallel-group RCTs generally raised concerns, primarily due to potential deviations from the intended interventions and the lack of blinding in outcome measurement **(Figure 2A)**. Additionally, using the ROBINS-I tool, both included split-face NRS showed an overall serious risk of bias. While the split-face design effectively reduced confounding related to patient-level characteristics, the absence of random side allocation resulted in a moderate risk of confounding. Also, both studies were open-label and used subjective outcome assessment using the global acne scarring system without blinding of outcome assessors, leading to a serious risk of bias in outcome measurement **(Figure 2B)**. Additionally, the certainty of evidence assessment is outlined in **(Table 3)**.

Primary Outcome: *Significant Clinical Improvement (>50%)*

Microneedling combined with topical insulin was associated with a significantly higher incidence of clinically significant improvement compared with microneedling combined with PRP (RR = 1.96, 95% CI [1.30–2.95], p < 0.0001) (**Figure 3A**). The pooled studies demonstrated no heterogeneity (I^2 = 0%). The leave-one-out sensitivity analysis confirmed the robustness of the findings, with consistent results observed across all iterations (**Figure 3B**). In the TSA, the cumulative Z-curve crossed the conventional boundary for statistical significance but did not cross the trial sequential monitoring boundary for benefit, and the required information size was not reached (**Figure 3C**). These findings indicate that the current evidence remains insufficient to draw definitive conclusions regarding the superiority of topical insulin over PRP, highlighting the need for additional well-designed trials. Subgroup analysis based on study design revealed no statistically significant difference between subgroups (p = 0.42), indicating that study design did not materially influence the observed overall effect **(Figure S1)**.

Secondary Outcomes

Change in Scar Severity Score

There was no significant difference between the microneedling plus insulin and microneedling plus PRP groups regarding the change in scar severity score (SMD = -0.52, 95% CI [-1.44, 0.39], p = 0.26, I^2 = 90.69%) **(Figure 4A)**. A leave-one-out sensitivity analysis indicated that the result became statistically significant, favoring insulin after omitting Ullah et al. (p = 0.02) **(Figure 4B)**. Subgroup analysis based on study design revealed no statistically significant difference between subgroups (p = 0.97), indicating that study design did not materially influence the observed overall effect **(Figure S2)**.

Patients' Satisfaction

Patient satisfaction largely followed the clinical efficacy data. Gahlot & Hussain reported that 48% of patients in the insulin group expressed excellent satisfaction, compared to only 8% in the PRP group [21]. In contrast, Ullah et al. reported significantly higher patient satisfaction scores in the PRP group (4.27 ± 0.79) compared to the insulin group (2.77 ± 0.68) [23].

Safety & Tolerability

None of the included studies reported episodes of symptomatic or biochemical hypoglycemia. Objective monitoring further supported this safety profile. Ullah et al. measured blood glucose levels before (88.88 mg/dL) and after the procedure (90.82 mg/dL) in the insulin group and found no statistically significant change [23]. Similarly, Mohta et al. and Pawar et al. monitored blood glucose levels 2 hours before and after the procedure and observed no clinically meaningful fluctuations, confirming the absence of systemic absorption [19, 22].

Regarding local tolerability, no statistically significant difference was observed between the microneedling plus insulin and microneedling plus PRP groups in the incidence of PIH (RR = 0.72, 95% CI [0.14–3.62], p = 0.69) (**Figure 5A**). The pooled analysis demonstrated no heterogeneity (I^2 = 0%). The leave-one-out sensitivity analysis confirmed the robustness of the findings, with consistent results across all iterations (**Figure 5B**). Subgroup analysis based on study design revealed no statistically significant difference between subgroups (p = 0.77), indicating that study design did not materially modify the overall effect (**Figure S3**).

Both interventions were generally well tolerated, with only mild and self-limiting adverse events, including transient erythema, edema, and procedural pain. Notably, Gahlot and Hussain reported a slightly lower incidence of local adverse effects in the insulin group compared with PRP (erythema: 8% vs 12%; edema: 8% vs 12%) [21], suggesting a potentially more favorable tolerability profile for topical insulin.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to directly compare the efficacy and safety of microneedling with topical insulin versus microneedling with autologous PRP for the treatment of atrophic post-acne scars. Overall, our primary analysis showed that patients treated with insulin achieved a higher rate of significant clinical improvement than those treated with PRP. Importantly, the advanced analysis (i.e., leave-one-out sensitivity analysis) further confirmed the

robustness of these findings. However, the TSA remained inconclusive, likely due to the limited overall sample size and the unmet required information size. In contrast, the initial analysis of continuous scar severity scores did not demonstrate a statistically significant difference between the two modalities, primarily because of substantial statistical heterogeneity and variability in the assessment tools used. Notably, after excluding one influential study [23], the overall effect size shifted in favor of insulin over PRP. From a safety perspective, both modalities exhibited excellent tolerability profiles. Taken together, however, the current evidence remains uncertain according to our GRADE certainty of evidence assessment.

The observed efficacy is likely due to insulin diffusing into micropunctures, providing sustained anabolic stimulation to dermal fibroblasts. This differs from PRP, in which growth factor release occurs as a single event and is rapidly degraded by proteolysis [32]. PRP works by delivering a supraphysiological concentration of autologous platelets, which degranulate to release a cocktail of growth factors, including PDGF, TGF-β, and VEGF [33]. This potent release is temporary, as tissue proteases often degrade these factors within hours to days [34]. In contrast, topical insulin may induce a more sustained biological effect. Insulin acts directly on the insulin receptor and insulin-like growth factor-1 receptor (IGF-1R) on keratinocytes and fibroblasts, triggering the phosphoinositide 3-kinase (PI3K)-Akt-mTOR signaling pathway [35]. Activation of the PI3K-Akt-mTOR pathway is essential for wound healing, as it inhibits apoptosis under cellular stress and promotes protein synthesis and cell migration [36]. Moreover, experimental models have demonstrated that insulin signaling accelerates keratinocyte migration into the wound bed [37].

Furthermore, insulin exerts a unique immunomodulatory effect that favors regeneration over fibrosis, as it promotes macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory and reparative M2 phenotype [38]. M2 macrophages play a critical role in secreting anti-inflammatory cytokines and regulating the deposition of organized collagen, rather than the parallel bundles typically observed in scar tissue [39]. Finally, insulin is also a potent angiogenic factor. By upregulating VEGF expression via the Akt pathway, topical insulin enhances local microcirculation within fibrotic tissue, thereby alleviating the local hypoxia that often contributes to atrophic scarring

[40]. Collectively, this triad of accelerated re-epithelialization, M2 macrophage polarization, and enhanced angiogenesis provides a strong biological rationale for the clinical improvement observed in our meta-analysis.

However, the pooled analysis of continuous scar severity scores did not reflect this clinical improvement, largely because of high statistical heterogeneity, which is mostly multifactorial. Methodologically, the included studies utilized different scar grading instruments, such as the Acne Scar Assessment Scale, Goodman & Baron's scale, and the Global Acne Scarring System, which inherently introduces variability when continuous changes are pooled. Additionally, there were notable differences in the study design (split-face versus parallel-group) and the treatment protocols. To clarify, microneedling depths ranged from 1.5 mm to 2.0 mm, and the number of treatment sessions ranged from 4 to 5. While differences in scar subtype distribution may also play a theoretical role in treatment responsiveness, the lack of baseline reporting of these subtypes in included studies prevents a definitive conclusion. Nonetheless, our sensitivity analysis demonstrated that removing Ullah et al. significantly reduced heterogeneity and shifted the continuous data toward insulin, aligning more closely with the primary clinical response data [23].

Moreover, the safety profile is critically important, particularly because most patients in the included studies (conducted in India and Pakistan) had Fitzpatrick skin types IV–VI [19–23]. Individuals with these skin types are at a substantially higher risk of PIH when treated with thermal modalities such as fractional CO_2 lasers, with reported rates ranging from 20% to 30% [10, 41]. In contrast, our analysis confirmed that microneedling represents a safer technique for skin of color, with low rates of adverse events observed in both treatment groups. Notably, the insulin group demonstrated zero reported cases of PIH across most included studies, whereas the PRP group showed only a very low incidence. Mechanistically, insulin exerts anti-inflammatory effects by suppressing oxidative stress and downregulating pro-inflammatory cytokines within the wound environment [42]. Additionally, topical insulin application is painless and non-traumatic, unlike PRP, which requires phlebotomy and often involves painful intradermal injections that may provoke localized inflammation and subsequent pigmentary alteration [22]. Collectively, these findings support

the favorable safety profile of both interventions, with a potential tolerability advantage for topical insulin.

According to the literature, Li et al. 2024 [43] conducted a network meta-analysis of 24 studies comparing microneedling alone versus its combination therapies and found that adjunctive treatments, including PRP, were superior to microneedling monotherapy. Similarly, Wu et al. 2025 [44], in a network meta-analysis of 68 RCTs, reported that laser combined with PRP or fillers achieved the greatest scar reduction, while laser plus chemical peeling yielded the highest patient satisfaction. However, insulin was not evaluated in these analyses, as all trials investigating microneedling with topical insulin were published thereafter. This highlights an important gap in the literature and underscores the need to consider microneedling combined with topical insulin as a potential therapeutic option in clinical practice.

Despite the novelty of our research question and the robustness of our methodology, our findings are subject to several limitations. First, the overall sample size was relatively small, limiting the statistical power of the analysis, as reflected in the TSA results. Second, reliance on subjective scar grading systems rather than objective profilometric assessments introduces the potential for measurement bias. Moreover, the open-label design of the included studies increases the risk of performance and detection bias, as both patients and evaluators were aware of treatment allocation. Third, the short follow-up periods (typically 2–3 months) precluded assessment of long-term collagen remodeling, which may continue for up to one year post-procedure [45]. Fourth, we were unable to stratify the analysis by scar subtype due to insufficient reporting across studies. Fifth, although we performed a subgroup analysis based on study design, the inclusion and pooling of different study designs (parallel-group and split-face studies) may still introduce methodological limitations that should be acknowledged. Finally, these methodological constraints collectively contributed to a low to very low certainty of evidence according to the GRADE framework.

From a clinical perspective, microneedling combined with topical insulin appears to be a promising, accessible, and well-tolerated alternative to PRP, particularly in patients with skin of color. Its favorable safety profile and ease of application may make it an attractive option in settings where

PRP preparation is costly or less feasible. Moving forward, future research should focus on adequately powered, double-blinded RCTs to confirm these findings. The incorporation of standardized and objective scar assessment tools, longer follow-up periods to evaluate sustained collagen remodeling, and stratification by scar subtype will be essential to better define its role in acne scar management.

CONCLUSION

Current evidence suggests that microneedling combined with topical insulin may yield a higher rate of clinical improvement than microneedling with autologous PRP, alongside a tolerable safety profile. Nevertheless, the inconclusive TSA, high heterogeneity, and low certainty of evidence prevent definitive conclusions regarding its efficacy. These preliminary findings highlight the critical need for additional large-scale, double-blinded RCTs that use objective assessments of scar severity to confirm the observed efficacy.

STATEMENTS AND DECLARATIONS

- Conflict of Interest statement: The authors declare that they have no conflicts of interest to disclose.
- Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.
- Informed consent: For this type of study, formal consent is not required.
- Declaration of Helsinki: All analyses were based on previously published studies conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

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TABLE AND FIGURE LEGENDS

Table 1. Summary characteristics of the included studies.

Table 2. Baseline characteristics of the participants.

Table 3. GRADE evidence profile summarizing the certainty of evidence for the included outcomes.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizing the study selection process.

Figure 2. Risk of bias assessment of included studies: **[A]** The upper panel shows the risk of bias of randomized controlled trials assessed using RoB-2 (low = green, some concerns = yellow, high = red). **[B]** The lower panel shows the risk of bias of the non-randomized split-face study assessed using ROBINS-I (low = green, moderate/unclear = yellow, high = red).

Figure 3. (A) Forest plot of the meta-analysis, **(B)** leave-one-out sensitivity analysis, and **(C)** trial sequential analysis demonstrating significant clinical improvement. CI = confidence interval; PRP = platelet-rich plasma.

Figure 4. (A) Forest plot of the meta-analysis and **(B)** leave-one-out sensitivity analysis demonstrating the mean change in scar severity score. SMD = standardized mean difference; CI = confidence interval; PRP = platelet-rich plasma.

Figure 5. (A) Forest plot of the meta-analysis and **(B)** leave-one-out sensitivity analysis demonstrating the incidence of PIH. CI = confidence interval; PRP = platelet-rich plasma; PIH = post-inflammatory hyperpigmentation.

SUPPLEMENTARY MATERIALS CONTENTS

Table S1. Search strategy.

Table S2. Excluded records in full-text screening.

Figure S1. Subgroup analysis based on study design for clinically significant improvement. CI = confidence interval; PRP = platelet-rich plasma.

Figure S2. Subgroup analysis based on study design for change in scar severity score. SMD = standardized mean difference; CI = confidence interval; PRP = platelet-rich plasma.

Figure S3. Subgroup analysis based on study design for PIH. CI = confidence interval; PRP = platelet-rich plasma; PIH = post-inflammatory hyperpigmentation.

META-ANALYSIS

Microneedling with Topical Insulin versus Microneedling with Platelet-Rich Plasma for Post-Acne Scars: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

Running Title: Microneedling with Insulin or PRP for Acne Scars.

ABSTRACT

Background: Atrophic acne scarring is a prevalent and psychologically distressing sequela of acne vulgaris, often resulting from insufficient matrix remodeling and collagen loss. While microneedling is a safe treatment, its efficacy as a monotherapy is often limited. Autologous platelet-rich plasma (PRP) is the current gold standard adjuvant, but its high cost and invasiveness restrict its use. Topical insulin has emerged as a cost-effective, non-invasive alternative to promote wound healing.

Methods: A comprehensive search was conducted across PubMed, Web of Science, CENTRAL, Scopus, and Google Scholar for comparative studies published up to January 2026. Risk of bias was assessed using the RoB-2 and ROBINS-I tools. The primary outcome was significant clinical improvement (>50%). Secondary outcomes included changes in scar severity scores and adverse events. Risk ratios (RRs) and standardized mean differences (SMDs) were pooled with 95% confidence intervals (CIs). Trial sequential analysis was also performed.

Results: Five studies involving 256 patients were included. Microneedling with topical insulin was associated with a significantly higher rate of significant clinical improvement compared to PRP (RR = 1.96, 95% CI [1.30–2.95], $p < 0.0001$). However, the pooled analysis of changes in scar severity scores showed no significant difference between groups (SMD = -0.52, 95% CI [-1.44, 0.39], $p = 0.26$), with high heterogeneity. Regarding safety, there was no significant difference in the risk of post-inflammatory hyperpigmentation (RR = 0.72, 95% CI [0.14–3.62], $p = 0.69$), and no episodes of hypoglycemia were reported.

Conclusion: Microneedling with topical insulin may achieve a higher rate of significant clinical improvement than PRP, with a comparable safety profile. However, given the inconclusive trial sequential analysis, high heterogeneity, and low overall certainty of evidence, these findings should be interpreted with caution. Further adequately powered trials are required to confirm this preliminary signal.

Keywords: acne; insulin; meta-analysis; microneedling; PRP; platelet-rich plasma; scar.

Level of Evidence: Not applicable.

INTRODUCTION

Acne vulgaris, a common chronic inflammatory condition of the pilosebaceous unit, affects approximately 9.4% of the global population [1]. While the active phase of the disease is often transient, it commonly leads to permanent atrophic scarring, particularly in adolescent and young adult populations with a history of severe nodulocystic inflammation [2]. Atrophic scarring results from a distorted wound healing process, marked by insufficient matrix remodeling and the loss of dermal collagen [3]. This process has been reported to cause an imbalance in collagen subtypes, especially a higher proportion of fibrotic type-I collagen than the regenerative type-III collagen characteristic of healthy dermis [4, 5]. In addition to physical disfigurement, acne scarring is linked to significant psychological distress, including anxiety, depression, and social impairment, thereby requiring effective therapeutic interventions [6].

Standard skin renewal techniques, including fractional laser treatment and aggressive chemical peels, function by removing the outer layer of skin to encourage the reconstruction of the dermis [7]. Despite their effectiveness, these techniques carry significant risks of long-term erythema and post-inflammatory hyperpigmentation (PIH), especially among patients with Fitzpatrick skin types IV–VI [8, 9]. Accordingly, microneedling has emerged as a safer alternative. This method involves using fine needles to produce deliberate micro-injuries, which break down scar tissue, encourage the release of growth factors from platelets, and foster the new collagen synthesis without breaking the outer skin barrier [10]. However, microneedling monotherapy often yields gradual or modest results [11]. Hence, it is usually used with topical adjuvants to improve patient results by leveraging the micro-channels created by the needles for transdermal drug delivery [10].

Autologous Platelet-Rich Plasma (PRP) is widely used and established as an adjuvant for microneedling [12]. PRP is an autologous concentration of platelets that yields supraphysiological levels of bioactive proteins, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β). These components collectively promote fibroblast proliferation and collagen synthesis [12–15]. While the efficacy of PRP is widely recognized, its widespread use is constrained by high cost, the invasive venipuncture process, and

the need for dedicated centrifuges [16]. Therefore, topical insulin has recently been proposed as a cost-effective, non-invasive alternative [17]. Insulin exhibits structural resemblance to insulin-like growth factor-1 (IGF-1) and facilitates wound healing through the phosphatidylinositol 3-kinase signaling pathway [18]. This activation upregulates VEGF expression and normalizes collagen architecture.

The comparative efficacy of these two options remains controversial. While early split-face non-randomized studies (NRS) suggested that topical insulin might offer superior efficacy and cost-effectiveness [19, 20], subsequent randomized controlled trials (RCTs) have reported conflicting results, with some recent data favoring PRP for patient satisfaction and scar reduction [21–23]. Hence, this systematic review and meta-analysis aims to evaluate the efficacy and safety of microneedling with topical insulin versus microneedling with autologous PRP for the treatment of atrophic post-acne scars.

METHODS AND MATERIALS

Review Protocol and Reporting Style

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) [ID: CRD420261309180]. The study design and reporting adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24] and the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions [25]. Ethical approval was not required for this meta-analysis because it relied exclusively on previously published, publicly available studies.

Information Sources and Search Strategy

On 17th January 2026, a systematic literature search was performed across five major electronic databases: PubMed, Web of Science (WoS), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Google Scholar. The search strategy combined keywords related to the intervention and the condition: “("acne vulgaris" OR "cicatrix" OR “acne” OR "post-acne" OR

“postacne” OR "atrophic scar*" OR "acne scar*" OR "rolling scar*" OR "boxcar scar*" OR "ice pick scar*") AND (“microneedling” OR "micro-needling" OR “dermaroller” OR "skin needling" OR "percutaneous collagen induction" OR "collagen induction therapy" OR “PCI”) AND ("Insulin") AND ("platelet-rich plasma" OR "platelet rich plasma" OR “PRP” OR "platelet concentrate"). **Table S1** provides the detailed search strings and output for each database. To enhance the completeness of the systematic search, the reference lists of all included studies were manually reviewed, and trial registries (i.e., ClinicalTrials.gov, ICTRP) were searched. Additional sources (i.e., ResearchGate, medRxiv) were also examined to identify potentially eligible unpublished studies. When required, corresponding authors were contacted to obtain missing information or to clarify study details. No restrictions were imposed regarding language, country of origin, or publication status.

Eligibility Criteria

We included prospective studies, encompassing both parallel-group RCTs and split-face comparative designs, based on the following PICO framework:

- **Population (P):** adult patients with post-acne atrophic scars (ice-pick, boxcar, or rolling), regardless of skin type (Fitzpatrick I-VI).
- **Intervention (I):** microneedling combined with topical insulin application.
- **Control (C):** microneedling combined with PRP application.
- **Outcomes (O): primary outcomes:** significant clinical improvement in scar severity defined as at least > 50% improvement assessed via standardized scales, such as the Goodman & Baron quantitative/qualitative scale or acne scar assessment scale (ASAS). **Secondary outcomes:** change in scar severity scale, patient satisfaction score, and the incidence of adverse events (including pain, erythema, edema, and post-inflammatory hyperpigmentation).

Study Selection Process

Records were managed and screened using an electronic platform. Two investigators independently screened studies in a two-stage process, beginning with title and abstract screening, followed by full-

text assessment of potentially eligible articles. Disagreements were resolved through consensus. The same approach was applied during the risk of bias assessment and statistical analysis.

Data Extraction

A standardized Excel extraction form was developed and pilot-tested using a subset of eligible studies. The form captured data in three categories: (1) Study characteristics: study design (parallel vs. split-face), country, sample size, insulin protocol (dosage/concentration), PRP protocol (preparation method), microneedling protocol (device type and needle depth), treatment schedule, and follow-up duration; (2) Baseline demographics: age, gender, Fitzpatrick skin type, scar type distribution, and baseline scar severity scores; and (3) Outcome data: as mentioned above.

Data extraction was performed independently by at least two reviewers. The first author (EA) resolved discrepancies. For the primary dichotomous outcome (significant clinical improvement >50%), data were extracted as the number of responders exactly as categorized and reported by the original study investigators. We did not perform any continuous-to-binary data conversions. For continuous variables, to account for baseline imbalances across groups, we extracted the mean change from baseline (post-treatment minus pre-treatment scores) and their associated standard deviations.

Risk of Bias and Certainty of Evidence

At least two reviewers independently assessed the risk of bias for each included RCT. For parallel-group RCTs, we used the standard Cochrane Risk of Bias 2 (RoB-2) tool for individually randomized trials [26]. For split-face NRS, we used the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [27], evaluating bias across seven domains: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result.

Additionally, the overall certainty of the evidence was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [28, 29], which

considers limitations such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. All judgments were justified and documented, with disagreements resolved through a consensus-based process.

Effect Measures and Meta-Analysis

All statistical analyses were performed using Stata/SE software, version 19 (StataCorp). Dichotomous outcomes were analyzed using risk ratios (RR). Given the variability in the clinical scar assessment tools across the included trials, continuous outcomes were pooled using standardized mean differences (SMDs). We calculated 95% confidence intervals (CIs) for all estimates. For zero-cell values, a continuity correction of 0.5 was applied. A p-value < 0.05 was considered statistically significant. We employed a random-effects model (REML) in the primary analysis to account for observed heterogeneity in scar type and treatment protocols. Heterogeneity was assessed using the Chi-squared test and the I^2 statistic. To evaluate the robustness of the pooled estimates, a leave-one-out sensitivity analysis was performed, systematically removing each study to determine its influence on the overall effect size. Also, we conducted a predefined subgroup analysis based on the study design (parallel-group RCTs versus split-face comparative studies). Finally, publication bias could not be evaluated as we included fewer than 10 studies [30].

Trial Sequential Analysis

To assess the robustness of the findings and control for Type I and Type II errors, Trial Sequential Analysis (TSA) was conducted using the TSA software [31], examining the cumulative Z-curve against the monitoring boundaries. The Required Information Size (RIS) was calculated based on an overall two-sided Type I error (alpha) of 5%, a statistical power of 80%, and a control event rate of 18.0%. To avoid subjective assumptions regarding the anticipated intervention effect, we utilized the software's empirical estimate. We used an O'Brien-Fleming alpha-spending function to construct the monitoring boundaries, and the cumulative Z-curve was examined against them to determine whether the evidence was conclusive.

RESULTS

Search Results and Study Selection

A total of 123 records were retrieved from the initial literature search across five databases. After removing 17 duplicates, the remaining 106 articles were screened. Consequently, 93 studies were excluded for failing to meet the inclusion criteria. Thirteen articles were sought, of which one was not retrieved. Twelve studies were evaluated for eligibility by screening their full texts. Seven studies were excluded for various reasons **(Table S2)**. Finally, five studies were included in the review [19–23] **(Figure 1)**.

Characteristics of Included Studies

Five studies (three parallel-group RCTs and two split-face NRS), involving a total of 256 patients, were included in our analysis [19–23]. The three parallel-group RCTs enrolled 190 patients, while the two split-face NRS enrolled 66 patients. A key characteristic of the included cohorts was variation in skin phenotypes, with multiple studies specifically targeting Fitzpatrick skin types III-VI to assess safety and the risk of dyspigmentation. Detailed study designs and baseline patient data are summarized in **(Tables 1 and 2)**, respectively.

Risk of Bias and Certainty of Evidence

The parallel-group RCTs generally raised concerns, primarily due to potential deviations from the intended interventions and the lack of blinding in outcome measurement **(Figure 2A)**. Additionally, using the ROBINS-I tool, both included split-face NRS showed an overall serious risk of bias. While the split-face design effectively reduced confounding related to patient-level characteristics, the absence of random side allocation resulted in a moderate risk of confounding. Also, both studies were open-label and used subjective outcome assessment using the global acne scarring system without blinding of outcome assessors, leading to a serious risk of bias in outcome measurement **(Figure 2B)**. Additionally, the certainty of evidence assessment is outlined in **(Table 3)**.

Primary Outcome: *Significant Clinical Improvement (>50%)*

Microneedling combined with topical insulin was associated with a significantly higher incidence of clinically significant improvement compared with microneedling combined with PRP (RR = 1.96, 95% CI [1.30–2.95], p < 0.0001) (**Figure 3A**). The pooled studies demonstrated no heterogeneity (I^2 = 0%). The leave-one-out sensitivity analysis confirmed the robustness of the findings, with consistent results observed across all iterations (**Figure 3B**). In the TSA, the cumulative Z-curve crossed the conventional boundary for statistical significance but did not cross the trial sequential monitoring boundary for benefit, and the required information size was not reached (**Figure 3C**). These findings indicate that the current evidence remains insufficient to draw definitive conclusions regarding the superiority of topical insulin over PRP, highlighting the need for additional well-designed trials. Subgroup analysis based on study design revealed no statistically significant difference between subgroups (p = 0.42), indicating that study design did not materially influence the observed overall effect **(Figure S1)**.

Secondary Outcomes

Change in Scar Severity Score

There was no significant difference between the microneedling plus insulin and microneedling plus PRP groups regarding the change in scar severity score (SMD = -0.52, 95% CI [-1.44, 0.39], p = 0.26, I^2 = 90.69%) **(Figure 4A)**. A leave-one-out sensitivity analysis indicated that the result became statistically significant, favoring insulin after omitting Ullah et al. (p = 0.02) **(Figure 4B)**. Subgroup analysis based on study design revealed no statistically significant difference between subgroups (p = 0.97), indicating that study design did not materially influence the observed overall effect **(Figure S2)**.

Patients' Satisfaction

Patient satisfaction largely followed the clinical efficacy data. Gahlot & Hussain reported that 48% of patients in the insulin group expressed excellent satisfaction, compared to only 8% in the PRP group [21]. In contrast, Ullah et al. reported significantly higher patient satisfaction scores in the PRP group (4.27 ± 0.79) compared to the insulin group (2.77 ± 0.68) [23].

Safety & Tolerability

None of the included studies reported episodes of symptomatic or biochemical hypoglycemia. Objective monitoring further supported this safety profile. Ullah et al. measured blood glucose levels before (88.88 mg/dL) and after the procedure (90.82 mg/dL) in the insulin group and found no statistically significant change [23]. Similarly, Mohta et al. and Pawar et al. monitored blood glucose levels 2 hours before and after the procedure and observed no clinically meaningful fluctuations, confirming the absence of systemic absorption [19, 22].

Regarding local tolerability, no statistically significant difference was observed between the microneedling plus insulin and microneedling plus PRP groups in the incidence of PIH (RR = 0.72, 95% CI [0.14–3.62], p = 0.69) (**Figure 5A**). The pooled analysis demonstrated no heterogeneity (I^2 = 0%). The leave-one-out sensitivity analysis confirmed the robustness of the findings, with consistent results across all iterations (**Figure 5B**). Subgroup analysis based on study design revealed no statistically significant difference between subgroups (p = 0.77), indicating that study design did not materially modify the overall effect (**Figure S3**).

Both interventions were generally well tolerated, with only mild and self-limiting adverse events, including transient erythema, edema, and procedural pain. Notably, Gahlot and Hussain reported a slightly lower incidence of local adverse effects in the insulin group compared with PRP (erythema: 8% vs 12%; edema: 8% vs 12%) [21], suggesting a potentially more favorable tolerability profile for topical insulin.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to directly compare the efficacy and safety of microneedling with topical insulin versus microneedling with autologous PRP for the treatment of atrophic post-acne scars. Overall, our primary analysis showed that patients treated with insulin achieved a higher rate of significant clinical improvement than those treated with PRP. Importantly, the advanced analysis (i.e., leave-one-out sensitivity analysis) further confirmed the

robustness of these findings. However, the TSA remained inconclusive, likely due to the limited overall sample size and the unmet required information size. In contrast, the initial analysis of continuous scar severity scores did not demonstrate a statistically significant difference between the two modalities, primarily because of substantial statistical heterogeneity and variability in the assessment tools used. Notably, after excluding one influential study [23], the overall effect size shifted in favor of insulin over PRP. From a safety perspective, both modalities exhibited excellent tolerability profiles. Taken together, however, the current evidence remains uncertain according to our GRADE certainty of evidence assessment.

The observed efficacy is likely due to insulin diffusing into micropunctures, providing sustained anabolic stimulation to dermal fibroblasts. This differs from PRP, in which growth factor release occurs as a single event and is rapidly degraded by proteolysis [32]. PRP works by delivering a supraphysiological concentration of autologous platelets, which degranulate to release a cocktail of growth factors, including PDGF, TGF-β, and VEGF [33]. This potent release is temporary, as tissue proteases often degrade these factors within hours to days [34]. In contrast, topical insulin may induce a more sustained biological effect. Insulin acts directly on the insulin receptor and insulin-like growth factor-1 receptor (IGF-1R) on keratinocytes and fibroblasts, triggering the phosphoinositide 3-kinase (PI3K)-Akt-mTOR signaling pathway [35]. Activation of the PI3K-Akt-mTOR pathway is essential for wound healing, as it inhibits apoptosis under cellular stress and promotes protein synthesis and cell migration [36]. Moreover, experimental models have demonstrated that insulin signaling accelerates keratinocyte migration into the wound bed [37].

Furthermore, insulin exerts a unique immunomodulatory effect that favors regeneration over fibrosis, as it promotes macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory and reparative M2 phenotype [38]. M2 macrophages play a critical role in secreting anti-inflammatory cytokines and regulating the deposition of organized collagen, rather than the parallel bundles typically observed in scar tissue [39]. Finally, insulin is also a potent angiogenic factor. By upregulating VEGF expression via the Akt pathway, topical insulin enhances local microcirculation within fibrotic tissue, thereby alleviating the local hypoxia that often contributes to atrophic scarring

[40]. Collectively, this triad of accelerated re-epithelialization, M2 macrophage polarization, and enhanced angiogenesis provides a strong biological rationale for the clinical improvement observed in our meta-analysis.

However, the pooled analysis of continuous scar severity scores did not reflect this clinical improvement, largely because of high statistical heterogeneity, which is mostly multifactorial. Methodologically, the included studies utilized different scar grading instruments, such as the Acne Scar Assessment Scale, Goodman & Baron's scale, and the Global Acne Scarring System, which inherently introduces variability when continuous changes are pooled. Additionally, there were notable differences in the study design (split-face versus parallel-group) and the treatment protocols. To clarify, microneedling depths ranged from 1.5 mm to 2.0 mm, and the number of treatment sessions ranged from 4 to 5. While differences in scar subtype distribution may also play a theoretical role in treatment responsiveness, the lack of baseline reporting of these subtypes in included studies prevents a definitive conclusion. Nonetheless, our sensitivity analysis demonstrated that removing Ullah et al. significantly reduced heterogeneity and shifted the continuous data toward insulin, aligning more closely with the primary clinical response data [23].

Moreover, the safety profile is critically important, particularly because most patients in the included studies (conducted in India and Pakistan) had Fitzpatrick skin types IV–VI [19–23]. Individuals with these skin types are at a substantially higher risk of PIH when treated with thermal modalities such as fractional CO_2 lasers, with reported rates ranging from 20% to 30% [10, 41]. In contrast, our analysis confirmed that microneedling represents a safer technique for skin of color, with low rates of adverse events observed in both treatment groups. Notably, the insulin group demonstrated zero reported cases of PIH across most included studies, whereas the PRP group showed only a very low incidence. Mechanistically, insulin exerts anti-inflammatory effects by suppressing oxidative stress and downregulating pro-inflammatory cytokines within the wound environment [42]. Additionally, topical insulin application is painless and non-traumatic, unlike PRP, which requires phlebotomy and often involves painful intradermal injections that may provoke localized inflammation and subsequent pigmentary alteration [22]. Collectively, these findings support

the favorable safety profile of both interventions, with a potential tolerability advantage for topical insulin.

According to the literature, Li et al. 2024 [43] conducted a network meta-analysis of 24 studies comparing microneedling alone versus its combination therapies and found that adjunctive treatments, including PRP, were superior to microneedling monotherapy. Similarly, Wu et al. 2025 [44], in a network meta-analysis of 68 RCTs, reported that laser combined with PRP or fillers achieved the greatest scar reduction, while laser plus chemical peeling yielded the highest patient satisfaction. However, insulin was not evaluated in these analyses, as all trials investigating microneedling with topical insulin were published thereafter. This highlights an important gap in the literature and underscores the need to consider microneedling combined with topical insulin as a potential therapeutic option in clinical practice.

Despite the novelty of our research question and the robustness of our methodology, our findings are subject to several limitations. First, the overall sample size was relatively small, limiting the statistical power of the analysis, as reflected in the TSA results. Second, reliance on subjective scar grading systems rather than objective profilometric assessments introduces the potential for measurement bias. Moreover, the open-label design of the included studies increases the risk of performance and detection bias, as both patients and evaluators were aware of treatment allocation. Third, the short follow-up periods (typically 2–3 months) precluded assessment of long-term collagen remodeling, which may continue for up to one year post-procedure [45]. Fourth, we were unable to stratify the analysis by scar subtype due to insufficient reporting across studies. Fifth, although we performed a subgroup analysis based on study design, the inclusion and pooling of different study designs (parallel-group and split-face studies) may still introduce methodological limitations that should be acknowledged. Finally, these methodological constraints collectively contributed to a low to very low certainty of evidence according to the GRADE framework.

From a clinical perspective, microneedling combined with topical insulin appears to be a promising, accessible, and well-tolerated alternative to PRP, particularly in patients with skin of color. Its favorable safety profile and ease of application may make it an attractive option in settings where

PRP preparation is costly or less feasible. Moving forward, future research should focus on adequately powered, double-blinded RCTs to confirm these findings. The incorporation of standardized and objective scar assessment tools, longer follow-up periods to evaluate sustained collagen remodeling, and stratification by scar subtype will be essential to better define its role in acne scar management.

CONCLUSION

Current evidence suggests that microneedling combined with topical insulin may yield a higher rate of clinical improvement than microneedling with autologous PRP, alongside a tolerable safety profile. Nevertheless, the inconclusive TSA, high heterogeneity, and low certainty of evidence prevent definitive conclusions regarding its efficacy. These preliminary findings highlight the critical need for additional large-scale, double-blinded RCTs that use objective assessments of scar severity to confirm the observed efficacy.

STATEMENTS AND DECLARATIONS

- Conflict of Interest statement: The authors declare that they have no conflicts of interest to disclose.
- Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.
- Informed consent: For this type of study, formal consent is not required.
- Declaration of Helsinki: All analyses were based on previously published studies conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

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TABLE AND FIGURE LEGENDS

Table 1. Summary characteristics of the included studies.

Table 2. Baseline characteristics of the participants.

Table 3. GRADE evidence profile summarizing the certainty of evidence for the included outcomes.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizing the study selection process.

Figure 2. Risk of bias assessment of included studies: **[A]** The upper panel shows the risk of bias of randomized controlled trials assessed using RoB-2 (low = green, some concerns = yellow, high = red). **[B]** The lower panel shows the risk of bias of the non-randomized split-face study assessed using ROBINS-I (low = green, moderate/unclear = yellow, high = red).

Figure 3. (A) Forest plot of the meta-analysis, **(B)** leave-one-out sensitivity analysis, and **(C)** trial sequential analysis demonstrating significant clinical improvement. CI = confidence interval; PRP = platelet-rich plasma.

Figure 4. (A) Forest plot of the meta-analysis and **(B)** leave-one-out sensitivity analysis demonstrating the mean change in scar severity score. SMD = standardized mean difference; CI = confidence interval; PRP = platelet-rich plasma.

Figure 5. (A) Forest plot of the meta-analysis and **(B)** leave-one-out sensitivity analysis demonstrating the incidence of PIH. CI = confidence interval; PRP = platelet-rich plasma; PIH = post-inflammatory hyperpigmentation.

SUPPLEMENTARY MATERIALS CONTENTS

Table S1. Search strategy.

Table S2. Excluded records in full-text screening.

Figure S1. Subgroup analysis based on study design for clinically significant improvement. CI = confidence interval; PRP = platelet-rich plasma.

Figure S2. Subgroup analysis based on study design for change in scar severity score. SMD = standardized mean difference; CI = confidence interval; PRP = platelet-rich plasma.

Figure S3. Subgroup analysis based on study design for PIH. CI = confidence interval; PRP = platelet-rich plasma; PIH = post-inflammatory hyperpigmentation.

Figure 1

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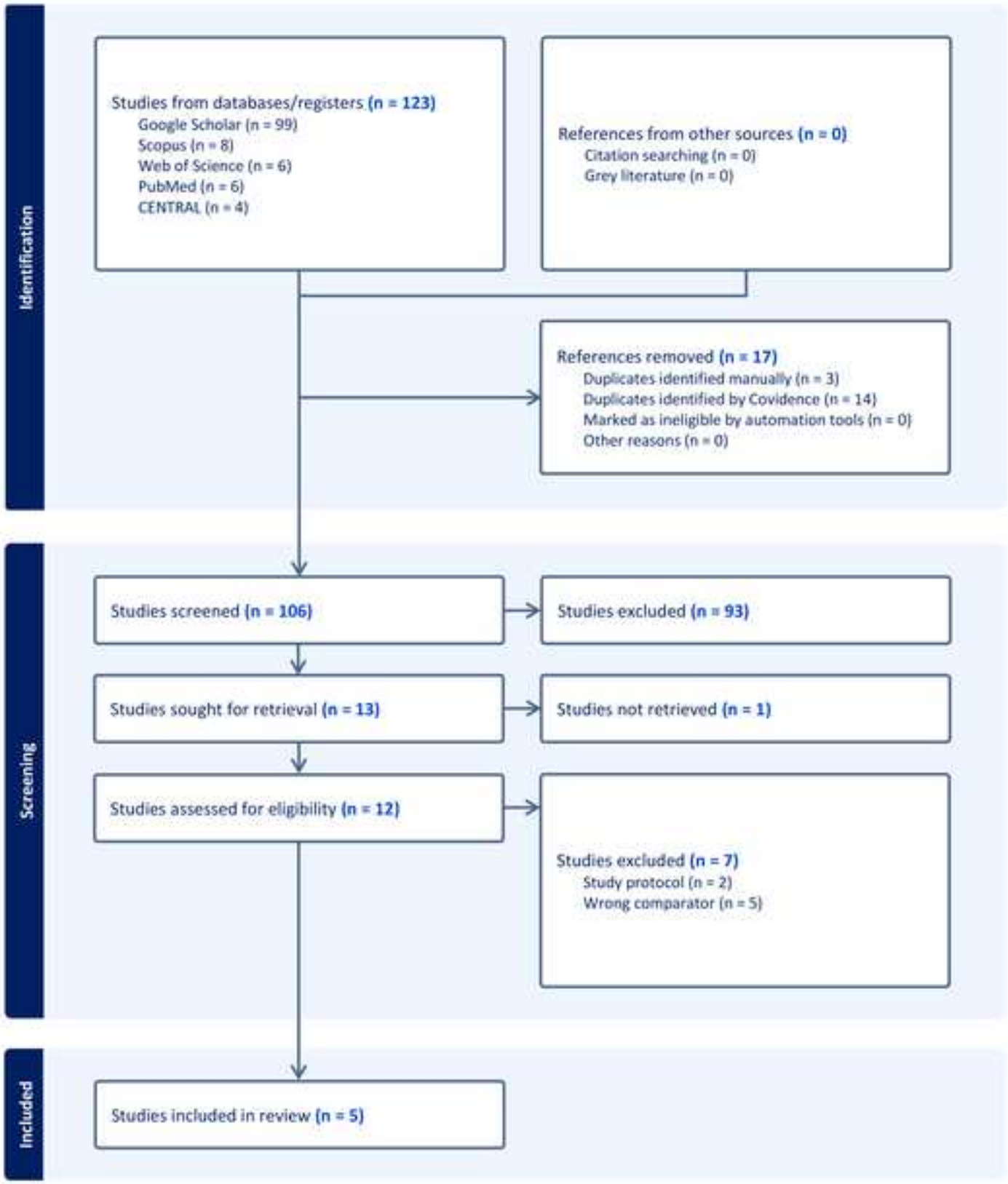

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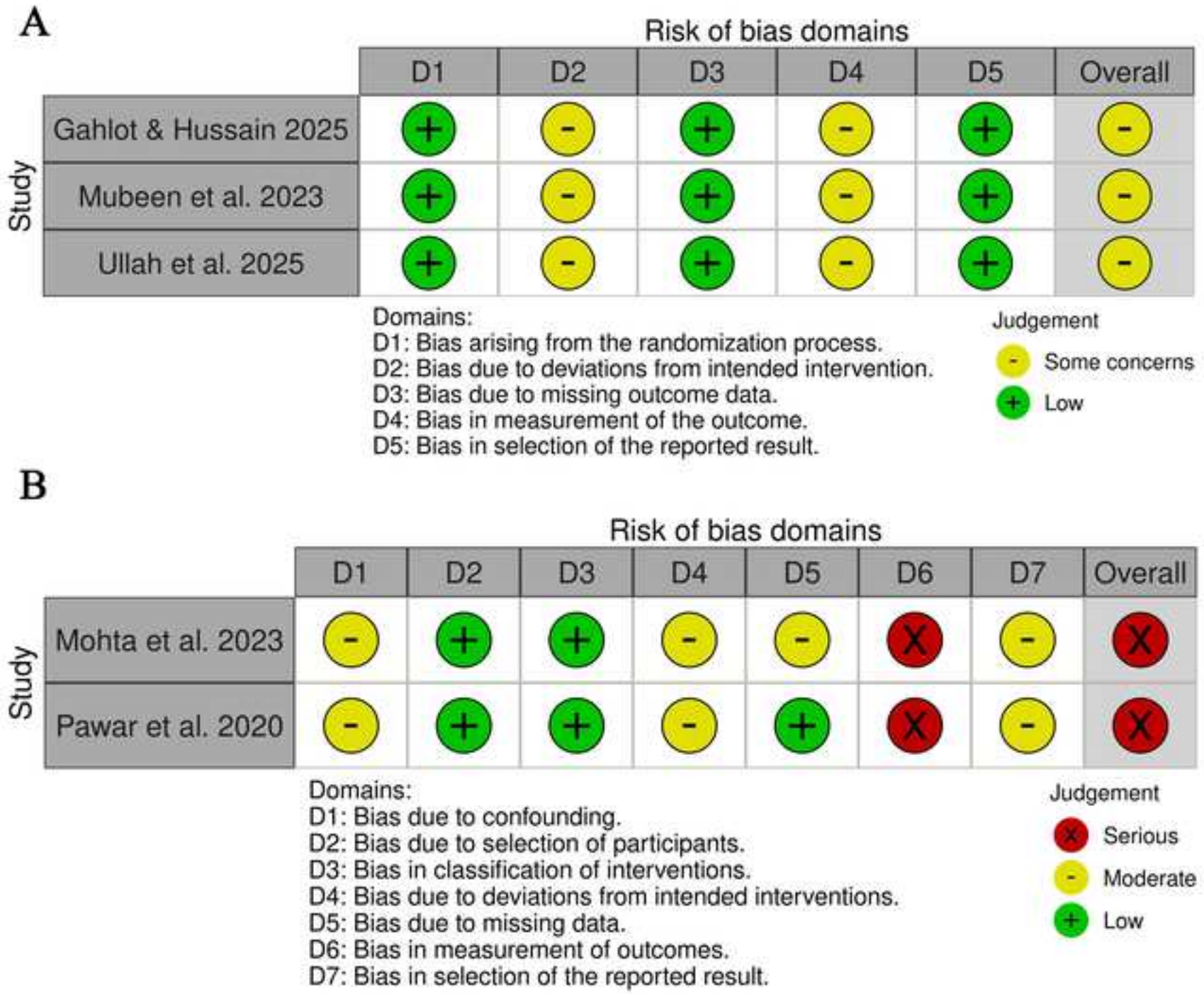

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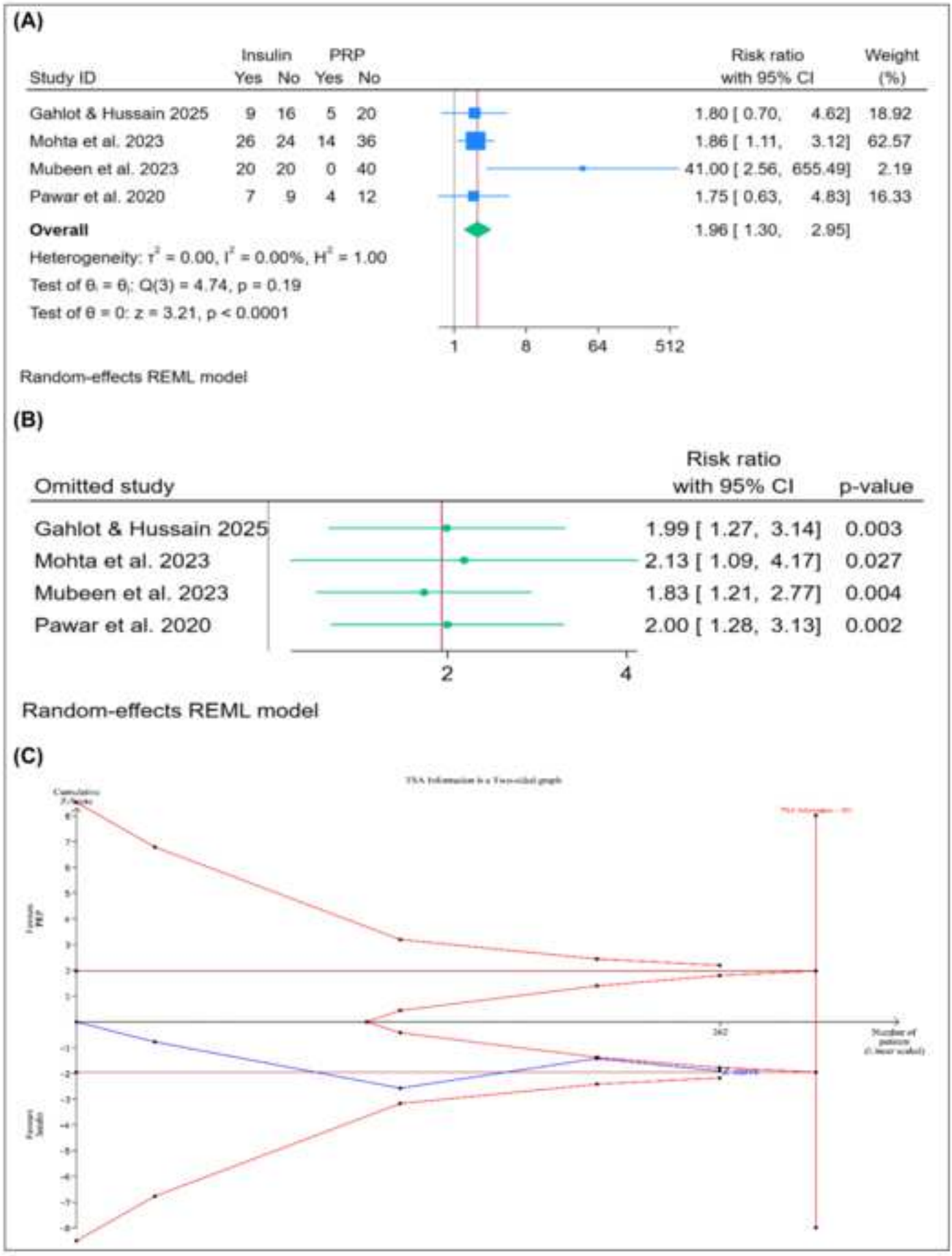

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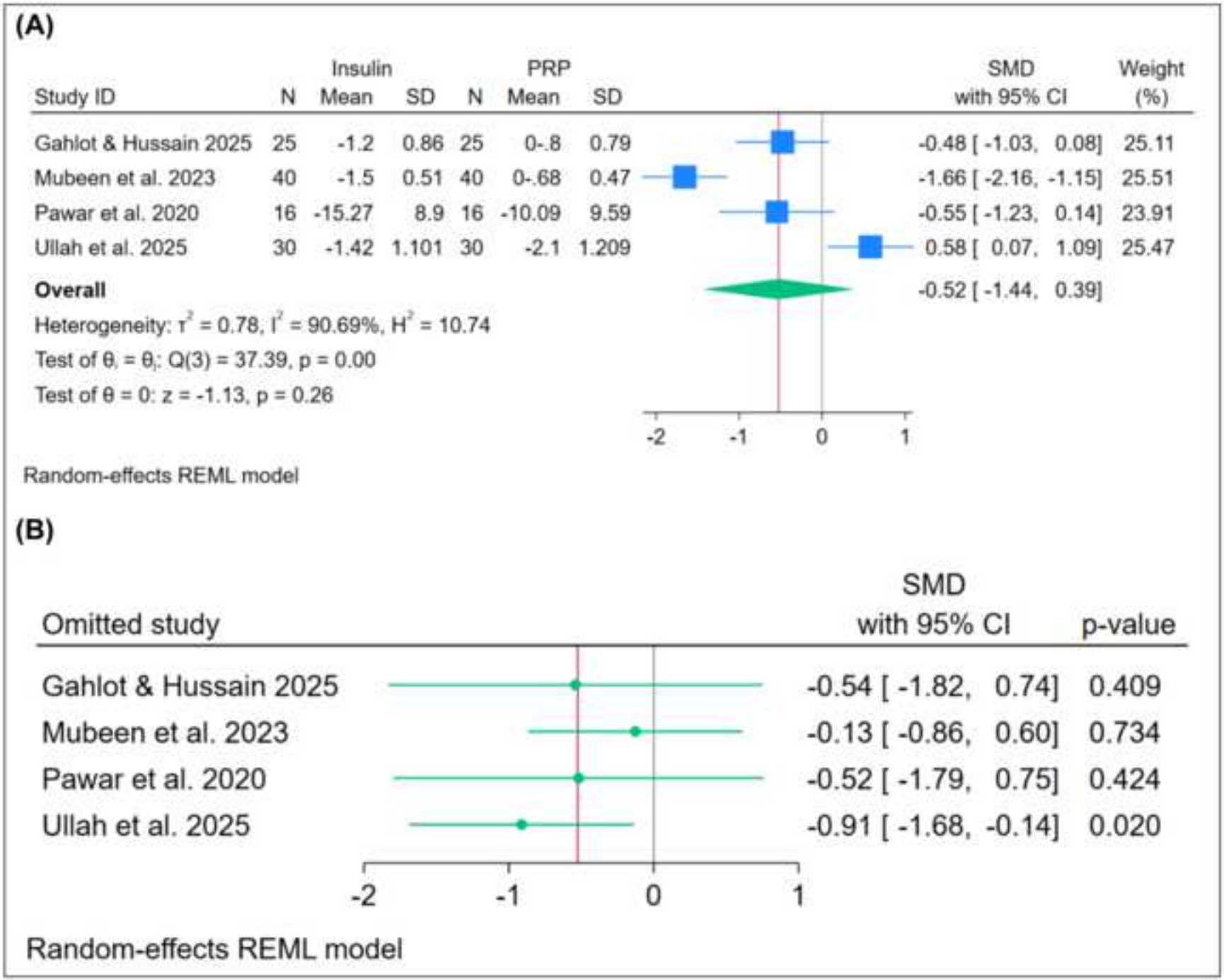

Figure 5

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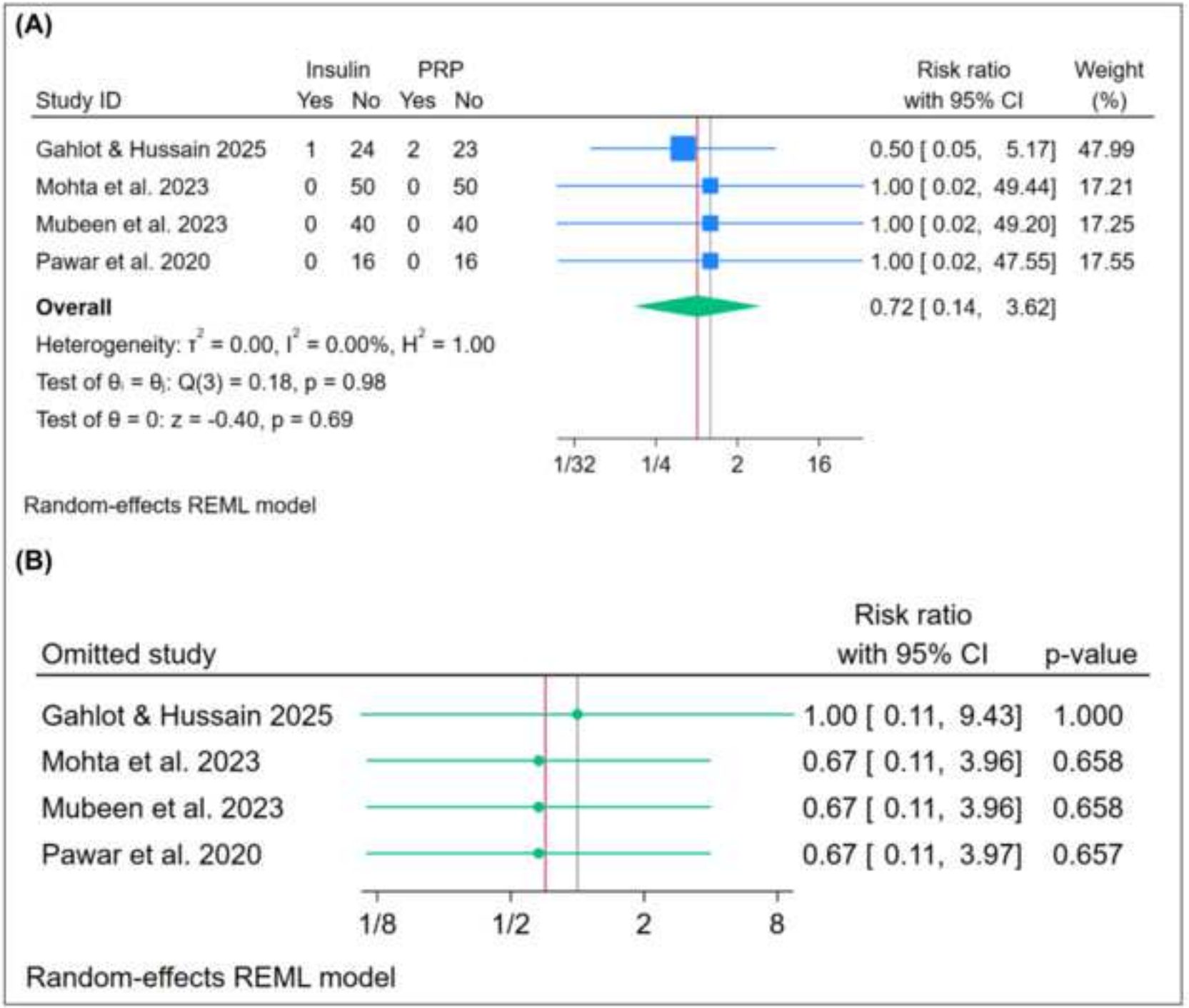

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Table 1. Summary characteristics of the included studies.

Study ID	Study Design	Country	N	Insulin Protocol	PRP Protocol	Microneedling Protocol	Treatment Schedule	Population / Skin Type	Scar Subtype	Primary Outcome	Follow-up Duration
Gahlot & Hussain 2025	Single-center, RCT	India	50	Topical application of regular human insulin (10 units Actrapid, 40 IU/mL)	Autologous PRP activated with calcium chloride	Motorized Pen (Dr. Pen Ultima A6), 2.0 mm depth	4 sessions at 3-week intervals	Age 18-35; Skin type not specified	Mixed (Ice pick, boxcar, and rolling)	Acne Scar Assessment Scale (ASAS) score	3 months after the last session
Mohta et al. 2023	Single-center, Split-face NRS	India	50	Topical application of 1–2 mL Human Actrapid Insulin (40 IU/mL solution)	Topical application of 1–2 mL Autologous PRP	Derma roller (192 needles), 1.5 mm depth	5 sessions at monthly intervals	Age unspecified; Fitzpatrick Skin Types III–VI	Mixed (Ice pick, boxcar, and rolling)	Global Acne Scarring System	3 months after the last session
Mubeen et al. 2023	Single-center, RCT	Pakistan	80	Topical application of 2 mL Human Actrapid Insulin	Topical application of 2 mL PRP	Derma roller (Depth not specified)	4 sessions at monthly intervals	Age 18-40; Fitzpatrick Skin Types IV–VI	Insulin: Ice pick: 2 (5%), Boxcar: 34 (85%), Rolling: 4 (10%); PRP: Ice pick: 5 (12.5%), Boxcar: 30 (75%), Rolling: 5 (12.5%)	Goodman and Baron's Qualitative Scale	2 months after the last session
Pawar et al. 2020	Single-center, Split-face NRS	India	16	Topical application of 1–2 mL Human Actrapid Insulin (40 IU/mL solution)	Topical application of 1–2 mL Autologous PRP	Dermaroller (192 needles), 1.5 mm depth	4 sessions at monthly intervals	Age 18-35; Fitzpatrick Skin Types IV–VI	Mixed (Ice pick, boxcar, and rolling)	Global Acne Scarring System	3 months after the last session

Ullah et al. 2025	Single-center RCT	Pakistan	60	Topical application of 2 mL Human Actrapid Insulin	Topical application of 2 mL Autologous PRP	NR	4 sessions at monthly intervals	Age 18-40; Fitzpatrick Skin Types I–V	Boxcar (80%); Ice pick and rolling also present, but the exact baseline numerical distribution NR	Scar severity scores (Scale not specified)	2 months after the last session

RCT: randomized controlled trial; PRP: platelet-rich plasma; ASAS: Acne Scar Assessment Scale; IU: international units; mL: milliliter; mm: millimeter; NR: not reported; NRS: non-randomized study.

Table 2. Baseline characteristics of the participants.

Study ID	Number of patients in each group		Age (Years), Mean (SD)		Gender (male), N. (%)		Fitzpatrick Skin Types, N. (%)		Scar Severity Score, Mean (SD)		Scar Duration, Mean (SD)	
	Microneedling + Insulin	Microneedling + PRP	Microneedling + Insulin	Microneedling + PRP	Microneedling + Insulin	Microneedling + PRP	Microneedling + Insulin	Microneedling + PRP	Microneedling + Insulin	Microneedling + PRP	Microneedling + Insulin	Microneedling + PRP
Gahlot & Hussain 2025	25	25	NR	NR	NR	NR	NR	NR	2.92 ± 0.93	3.16 ± 0.73	NR	NR
Mohta et al. 2023	50 (Split-face)		NR	NR	NR	NR	Types III–VI (100%)		NR	NR	NR	NR
Mubeen et al. 2023	40	40	23.68 ± 5.03	24.48 ± 4.75	10 (25.0%)	13 (32.5%)	IV: 35 (87.5%) V: 4 (10.0%) VI: 1 (2.5%)	IV: 36 (90.0%) V: 3 (7.5%) VI: 1 (2.5%)	Grade III: 13 (32.5%) Grade IV: 27 (67.5%)	Grade III: 11 (27.5%) Grade IV: 29 (72.5%)	4.5 ± 2.1 years	4.9 ± 2.3 years
Pawar et al. 2020	16 (Split-face)		24.69 ± 10.3		7 (43.8%)		Types IV–VI (100%)		NR	NR	NR	NR
Ullah et al. 2025	30	30	NR	NR	8 (26.7%)	13 (43.3%)	Types I–V (Mixed)		6.40 ± 1.07	6.42 ± 1.09	28.57 ± 15.62 months	31.80 ± 14.90 months

PRP: platelet-rich plasma; SD: standard deviation; N: number; NR: not reported.

Table 3. GRADE evidence profile summarizing the certainty of evidence for the included outcomes.

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**With [Microneedling + PRP]**	**With [Microneedling + Insulin]**	**Relative effect (95% CI)**	**Risk with [Microneedling + PRP]**	**Risk difference with [Microneedling + Insulin]**
Significant Clinical Improvement											
196 patients / 262 faces (4 studies)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low[a,b]	23/131 (17.6%)	62/131 (47.3%)	**RR 1.96** (1.30 to 2.95)	23/131 (17.6%)	**169 more per 1,000** (from 53 more to 342 more)
Change in Scar Severity Score											
206 patients / 222 faces (4 studies)	serious[a]	very serious[c]	not serious	very serious[d]	none	⨁◯◯◯ Very low[a,c,d]	111	111	-	-	SMD **0.52 SD lower** (1.44 lower to 0.39 higher)
Post-Inflammatory Hyperpigmentation											
196 patients / 262 faces (4 studies)	serious[a]	not serious	not serious	very serious[e]	none	⨁◯◯◯ Very low[a,e]	2/131 (1.5%)	1/131 (0.8%)	**RR 0.71** (0.15 to 3.52)	2/131 (1.5%)	**4 fewer per 1,000** (from 13 fewer to 38 more)

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference; **Explanations:**
a. All studies showed either some concerns or a high risk of bias.

b. A low number of events.

c. $I^2 > 50\%$.

d. A wide confidence interval that does not exclude the appreciable harm or benefit, with a low number of participants.

e. A wide confidence interval that does not exclude the appreciable harm or benefit, with a low number of events.

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