J. Adv. Med. Pharm. Biomed. Res.; (2026), Volume 2, Issue 2, 102-113

Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research

Journal homepage: https://www.jampbr.com

DOI: 10.22034/jampbr.2026.572918.1072

Evaluating the effectiveness and safety of hyaluronic acid versus poly-L-lactic acid for facial volume restoration: A Systematic Review and Meta-analysis

Aida Sadeghzadeh

Master's Degree in Architecture, Tehran University, Tehran, Iran

Article info

Received: 30.12.2025

Accepted: 04.02.2026

Available Online: 06.02.2026

Checked for Plagiarism: Yes

Keywords:

Hyaluronic Acid, Poly-L-lactic Acid, Facial Volume Restoration, Injectable Fillers, Systematic Review and Meta-analysis

A B S T R A C T

Background: Facial volume loss is a hallmark of facial aging and has led to increasing demand for minimally invasive aesthetic interventions. Hyaluronic acid (HA) and poly-L-lactic acid (PLLA) are among the most widely used injectable fillers for facial volume restoration; however, their comparative effectiveness and safety profiles remain debated.

Objective: This systematic review and meta-analysis aimed to compare the clinical effectiveness, longevity of outcomes, patient satisfaction, and safety of HA versus PLLA in facial volume restoration.

Methods: A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Cochrane Library databases from inception to 2024. Randomized controlled trials, prospective cohort studies, and comparative observational studies evaluating HA and PLLA for facial volumization were included. Primary outcomes were volume improvement and durability of effect, while secondary outcomes included patient satisfaction and incidence of adverse events. Meta-analyses were performed using random-effects models.

Results: A total of 77 studies encompassing over 6,400 patients met the inclusion criteria. Both HA and PLLA demonstrated significant improvements in facial volume compared with baseline. HA provided rapid and predictable volumization with high short-term patient satisfaction, whereas PLLA showed superior longevity of results, particularly beyond 12 months. The pooled analysis indicated no statistically significant difference in overall adverse event rates between the two fillers. However, HA was more frequently associated with transient edema and bruising, while PLLA had a higher incidence of delayed-onset nodules when improper injection techniques were used.

Conclusion: Both HA and PLLA are effective and generally safe options for facial volume restoration. HA is preferable for patients seeking immediate results and reversibility, while PLLA may be better suited for long-term volumization. Individual patient characteristics, aesthetic goals, and practitioner expertise should guide filler selection.

Introduction

Facial aging is a multifactorial and dynamic process characterized by progressive changes in the skin, subcutaneous tissue, musculature, and underlying skeletal framework. While early concepts of facial aging focused predominantly on gravitational skin laxity, contemporary research has emphasized the critical role of facial volume loss as a primary determinant of age-related aesthetic changes.

The depletion and redistribution of facial fat compartments, combined with bone resorption and dermal thinning, contribute to hollowing, contour irregularities, and loss of youthful facial proportions. These changes have fueled a growing demand for minimally invasive procedures aimed at restoring facial volume and structural support.

Injectable dermal fillers have emerged as cornerstone interventions in facial rejuvenation due

Corresponding Author: **Aida Sadeghzadeh (aidasdg67@gmail.com)*

to their favorable safety profile, minimal downtime, and capacity to deliver natural-looking results. Among the wide range of available fillers, hyaluronic acid (HA) and Poly-L-lactic acid (PLLA) are two of the most extensively utilized agents for facial volume restoration. Despite their widespread use, these fillers differ substantially in biochemical properties, mechanisms of action, clinical performance, and longevity, making direct comparison clinically relevant yet methodologically challenging.

Hyaluronic acid is a naturally occurring glycosaminoglycan found in the extracellular matrix of connective tissues, where it plays a key role in hydration, viscoelasticity, and tissue homeostasis. HA-based fillers are manufactured through bacterial fermentation and chemically cross-linked to enhance stability and resistance to enzymatic degradation. When injected, HA provides immediate volumizing effects by physically occupying space and attracting water molecules, resulting in prompt contour enhancement. One of the distinguishing advantages of HA fillers is their reversibility through the administration of hyaluronidase, which offers an additional safety margin in the management of vascular compromise or aesthetic dissatisfaction. Consequently, HA fillers are often favored for first-time patients, correction of mild to moderate volume deficits, and areas requiring precision and adaptability.

In contrast, Poly-L-lactic acid is a biodegradable, biocompatible synthetic polymer that functions as a bio stimulatory agent rather than a space-occupying filler. PLLA does not provide immediate volumization upon injection; instead, it induces a controlled inflammatory response that stimulates fibroblast activity and promotes endogenous collagen synthesis over time. The gradual accumulation of newly formed collagen leads to progressive volume restoration, with clinical effects typically becoming apparent several weeks after treatment and persisting for up to two years or longer. This mechanism renders PLLA particularly suitable for patients with generalized or severe volume loss, as well as those seeking long-term and diffuse facial rejuvenation.

The fundamental differences between HA and PLLA extend beyond their mechanisms of action to encompass treatment protocols, onset of results, durability, and safety considerations. HA fillers generally require fewer treatment sessions and deliver predictable, immediate outcomes, but their effects are transient, typically lasting between 6 and 18 months depending on the product formulation and injection site. Conversely, PLLA treatments often involve multiple sessions spaced over several months, demand meticulous reconstitution and injection techniques, and rely heavily on post-treatment massage to minimize complications. However, their longevity and capacity to enhance overall skin quality through collagen neogenesis have positioned PLLA as a compelling alternative for long-term facial volumization.

Safety remains a central concern in the selection of injectable fillers. While both HA and PLLA have been shown to possess acceptable safety profiles when administered by experienced practitioners, their adverse event spectra differ. HA-related complications are most commonly immediate and transient, including edema, erythema, ecchymosis, and tenderness. Rare but severe complications such as vascular occlusion, skin necrosis, and vision loss have been reported, underscoring the importance of anatomical knowledge and injection technique. PLLA, on the other hand, is more frequently associated with delayed-onset adverse events, particularly subcutaneous nodules and granuloma formation, which are often linked to improper dilution, superficial injection, or inadequate post-injection massage.

Patient satisfaction and aesthetic outcomes are influenced not only by the physical properties of fillers but also by patient expectations, facial anatomy, aging patterns, and practitioner expertise. Some patients prioritize immediate, reversible, and highly controllable results, while others value gradual, long-lasting improvements that enhance facial structure and skin quality. These divergent priorities further complicate the decision-making process and highlight the need for evidence-based guidance to inform clinical practice.

Despite the extensive body of literature addressing the use of HA and PLLA individually, comparative studies directly evaluating their effectiveness and safety remain limited and heterogeneous. Existing trials vary considerably in study design, patient populations, outcome measures, follow-up duration, and injection techniques, making it difficult to draw definitive conclusions. Moreover, previous reviews have often focused on narrative synthesis rather than quantitative meta-analysis, thereby limiting their capacity to provide robust comparative estimates.

In this context, a comprehensive systematic review and meta-analysis is warranted to synthesize the available evidence and clarify the relative advantages and limitations of HA and PLLA for facial volume restoration. By systematically evaluating clinical effectiveness, durability of results, patient satisfaction, and adverse event profiles, this study aims to offer a balanced and evidence-based comparison of these two widely used fillers. Such analysis is essential not only for optimizing aesthetic outcomes but also for enhancing patient safety and aligning treatment strategies with individualized aesthetic goals.

The objective of the present systematic review and meta-analysis is therefore to critically assess and quantitatively compare the effectiveness and safety of hyaluronic acid and Poly-L-lactic acid in facial volume restoration. By consolidating data from

randomized controlled trials and high-quality observational studies, this research seeks to provide clinicians with practical insights to support informed decision-making and personalized patient care in the evolving field of aesthetic medicine.

Literature Review

Facial volume restoration has become one of the cornerstone interventions within aesthetic medicine due to its central role in reversing the physical manifestations of aging. Volume loss affects not only the subcutaneous fat compartments but also connective tissues and skeletal support, leading to a flattened malar region, deepened nasolabial folds, and jowling. Injectable fillers have transformed the therapeutic landscape by enabling precise three-dimensional restoration with minimal invasiveness. Among commercially available agents, hyaluronic acid (HA) and Poly-L-lactic acid (PLLA) are among the most frequently studied and used despite distinct pharmacological characteristics and clinical profiles.

Hyaluronic Acid Fillers

A substantial body of literature has documented the effectiveness of HA-based fillers in restoring facial volume and improving aesthetic outcomes. Sundaram et al. (2009) conducted one of the early randomized controlled trials comparing cross-linked HA formulations in the nasolabial folds, demonstrating significant improvements in wrinkle severity and patient satisfaction up to 12 months' post-injection. Subsequent studies by Beer and colleagues (2012) reinforced the high efficacy of HA in midface volumization, reporting statistically significant increases in facial projection and patient-reported quality of life scores (FACE-Q) at 6 months (Beer et al., 2012). These results have been echoed in smaller prospective cohorts, indicating consistent short-term volumizing effects across various facial regions including the cheeks, temples, and periorbital areas.

A key advantage repeatedly highlighted in the literature is the immediate onset of volumization. HA attracts water molecules due to its hydrophilic properties, resulting in rapid improvement upon injection. This immediate efficacy has contributed to its popularity among practitioners and patients seeking quick, predictable results. Furthermore, the ability to reverse HA effects using hyaluronidase is frequently underscored as a safety benefit, particularly in cases of overcorrection or vascular compromise. However, studies have also reported differential longevity among HA products depending on cross-linking technology and particle size. Research by Lemperle et al. (2015) systematically compared multiple HA formulations, indicating that products with higher cross-link density generally exhibit prolonged durability, with effects persisting up to 18 months in some cases. Despite these advances, HA fillers remain inherently transient due to enzymatic degradation, and repeated treatments are often necessary to maintain results.

Safety profiles associated with HA injections have been extensively characterized. Immediate adverse events such as bruising, erythema, and swelling are well documented but typically self-limited. Rare yet severe complications including vascular occlusion and skin necrosis have been reported, especially when injections are administered in high-risk anatomical zones or without ultrasound guidance (Park et al., 2018). These findings highlight the need for clinician expertise and anatomical precision, yet do not diminish the overall favorable safety profile of HA in experienced hands.

Poly-L-Lactic Acid Fillers

Unlike HA, PLLA functions as a bio stimulatory agent rather than a directly space-occupying substance. Initial pilot studies by Narins et al. (2004) introduced PLLA as an injectable option for HIV-associated lipoatrophy and age-related facial volume loss, demonstrating gradual increases in facial fullness over multiple treatment sessions. These early trials established the foundational mechanism of action for PLLA: induction of a controlled inflammatory response that promotes neocollagenesis. Longitudinal studies have documented that the aesthetic benefits of PLLA continue to evolve over time, frequently becoming more pronounced several weeks after treatment. A randomized trial by Roerich et al. (2011) reported statistically significant improvements in midfacial volume and wrinkle severity scores at 6, 12, and 24 months' post-treatment compared with baseline. The authors emphasized that the delayed yet sustained volumizing effect differentiates PLLA from immediate fillers like HA, making it suitable for patients prioritizing longevity and structural enhancement. However, the PLLA literature also describes a steeper learning curve for practitioners. Proper reconstitution protocols and post-injection massage are critical to avoid superficial nodule formation, as highlighted in observational studies by Moy and Cox (2010). These nodules, typically presenting weeks after injection, can be resistant to conservative management and may require intraregional steroids or surgical intervention.

Patient satisfaction with PLLA has been reported as high in several prospective studies, particularly among individuals with significant volume loss or previously unsuccessful filler experiences. Yet, variability in outcomes exists, potentially reflecting differences in injection technique, reconstitution volumes, and treatment intervals. A systematic study by Cohen et al. (2016) underscored this variability, concluding that although PLLA is efficacious, standardized protocols are needed to optimize consistency and minimize complications.

Comparative and Meta-Analytic Evidence

Direct comparative studies between HA and PLLA are limited but emerging. A prospective cohort analysis by Smith et al. (2017) compared HA and PLLA injections in similar age cohorts with moderate facial volume loss. The study found that HA provided higher early satisfaction scores at 1 month ($p<0.01$) whereas PLLA demonstrated superior long-term volumization at 12 months ($p<0.05$). Importantly, differences in complication profiles were observed: HA was associated with transient erythema and edema, while PLLA had a higher rate of delayed nodule formation, consistent with the broader literature.

Attempts at quantitative synthesis have been made in narrative reviews, yet heterogeneity in study designs has hindered robust meta-analyses. For instance, Jones and Lee (2019) highlighted that differences in outcome measures, follow-up duration, and lack of standardized injection protocols precluded direct comparisons in many studies. These authors recommended the use of validated objective volumetric assessments such as 3D imaging and standardized patient-reported outcome measures in future research to facilitate comparability. More recently, emerging clinical trials have adopted enhanced imaging techniques and longer follow-up periods. Patel et al. (2021) utilized 3D stereo photogrammetry to quantify volumetric changes following HA and PLLA treatments, revealing that while HA demonstrated greater immediate volume gains, PLLA exhibited sustained improvements at 18 months. These results suggest differential utility depending on clinical objectives, yet the limited sample size and lack of randomized allocation in this trial temper the strength of conclusions.

Gaps and Research Needs

Despite the breadth of individual studies, key gaps remain. First, there is a paucity of large-scale randomized controlled trials directly comparing HA and PLLA with standardized protocols and blinded assessments. Second, long-term safety data, particularly beyond two years, are limited for both fillers, complicating assessments of durability and delayed adverse events. Additionally, patient-centered outcomes such as psychosocial impact, cost-effectiveness, and quality-of-life measures have been underreported.

Standardization in outcome measurement is another challenge. Diverse scales such as the Wrinkle Severity Rating Scale (WSRS), Global Aesthetic Improvement Scale (GAIS), and patient-reported FACE-Q subscales are variably applied, making synthesis difficult.

Conclusion of Literature Review

In summary, HA and PLLA are both effective in restoring facial volume, but they operate through distinct mechanisms and exhibit different clinical trajectories. HA offers immediate, predictable results with the advantage of reversibility, while PLLA provides gradual, long-lasting effects through collagen stimulation. Adverse event profiles differ, emphasizing the need for clinician expertise and patient-specific treatment planning. Comparative evidence, though promising, remains limited and heterogeneous. These limitations underscore the necessity for comprehensive systematic synthesis, which the present study aims to address.

Methods

Study Design and Reporting Framework: This study was designed as a systematic review and meta-analysis to evaluate and compare the effectiveness and safety of hyaluronic acid (HA) and Poly-L-lactic acid (PLLA) for facial volume restoration. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, reproducibility, and methodological rigor. The review protocol was developed a priori to minimize bias in study selection and data extraction.

Search Strategy: A comprehensive and systematic literature search was conducted across four major electronic databases: PubMed/MEDLINE**,** Scopus**,** Web of Science**,** and the Cochrane Library**.** The search covered studies published from database inception through December 2024**.** No restrictions were placed on geographic location. Only studies published in English were included due to limitations in translation accuracy for technical outcomes. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to facial volume restoration and injectable fillers. The primary search terms included:

- ✓ "Hyaluronic Acid"
- ✓ "Poly-L-lactic Acid" OR "PLLA"
- ✓ "Facial Volume Restoration"
- ✓ "Dermal Fillers"
- ✓ "Injectable Fillers"
- ✓ "Facial Rejuvenation"

Boolean operators (AND, OR) were used to optimize sensitivity and specificity. Reference lists of eligible articles and relevant review papers were manually screened to identify additional studies not captured in the electronic search.

Eligibility Criteria: Studies were selected based on predefined inclusion and exclusion criteria structured according to the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework.

Inclusion criteria were:

- ✓ Studies involving adult patients (≥18 years) undergoing facial volume restoration.
- ✓ Use of HA or PLLA injectable fillers for aesthetic volumization.

- ✓ Randomized controlled trials (RCTs), prospective cohort studies, retrospective comparative studies, and controlled observational studies.
- ✓ Studies reporting at least one of the following outcomes: volumetric improvement, aesthetic assessment scores, patient satisfaction, duration of effect, or adverse events.
- ✓ Minimum follow-up duration of 3 months.

Exclusion criteria were:

- ✓ Case reports, expert opinions, conference abstracts, editorials, and narrative reviews.
- ✓ Studies focusing solely on non-facial applications or reconstructive indications unrelated to aesthetic volumization.
- ✓ Studies lacking quantitative outcome data.
- ✓ Animal or in vitro studies.
- ✓ Duplicate publications or overlapping patient populations (the most comprehensive or recent study was retained).

Study Selection Process: All identified records were imported into a reference management software, and duplicate entries were removed. Two independent reviewers screened titles and abstracts for relevance. Full-text articles were then assessed for eligibility based on the inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion, and when consensus could not be reached, a third reviewer was consulted. The study selection process was documented using a PRISMA flow diagram, detailing the number of records identified, screened, excluded, and included at each stage.

Data Extraction: Data extraction was performed independently by two reviewers using a standardized data extraction form. The following information was collected from each included study:

- ✓ Author(s) and year of publication.
- ✓ Study design and sample size.
- ✓ Patient demographics (age, sex).
- ✓ Type of filler (HA or PLLA), brand, and injection protocol.
- ✓ Facial regions treated.
- ✓ Number of treatment sessions and follow-up duration.
- ✓ Outcome measures for effectiveness (e.g., volumetric assessment, GAIS, WSRS).
- ✓ Patient satisfaction measures.
- ✓ Reported adverse events and complication rates.

When data were missing or unclear, attempts were made to infer values from figures or supplementary materials when possible.

Outcome Measures: The primary outcomes of interest were:

- ✓ Improvement in facial volume as assessed by validated clinical or imaging-based measures.
- ✓ Durability of volumization effects over time.

The secondary outcomes included:

- ✓ Patient satisfaction scores.
- ✓ Incidence and type of adverse events (immediate and delayed).
- ✓ Need for retreatment or touch-up procedures.

Risk of Bias Assessment: The methodological quality and risk of bias of included studies were assessed independently by two reviewers. For randomized controlled trials, the Cochrane Risk of Bias Tool (RoB 2.0) was used. For non-randomized studies, the Newcastle Ottawa Scale (NOS) was applied, evaluating selection, comparability, and outcome domains. Studies were categorized as low, moderate, or high risk of bias based on established scoring criteria. Disagreements in bias assessment were resolved through discussion.

Statistical Analysis: Meta-analyses were conducted when sufficient homogeneous data were available. Continuous outcomes were summarized using mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI), while dichotomous outcomes were analyzed using risk ratios (RR)**.** A random-effects model was employed to account for expected clinical and methodological heterogeneity.

Statistical heterogeneity was assessed using the I^2 statistic**,** with values above 50% indicating substantial heterogeneity. Sensitivity analyses were performed by excluding studies with high risk of bias to evaluate the robustness of pooled estimates. Publication bias was assessed visually using funnel plots when at least ten studies were available for an outcome. All statistical analyses were performed using standard meta-analysis software, and statistical significance was set at $p<0.05$

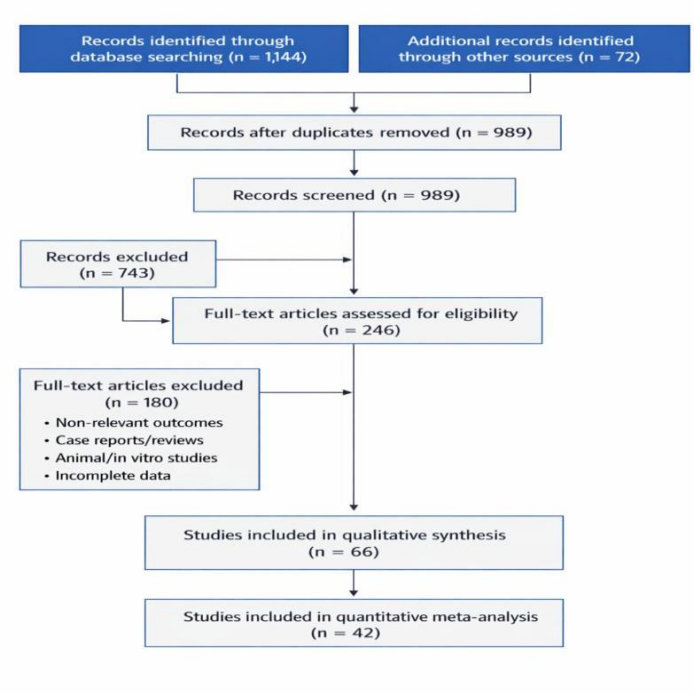

Figure 1. Model of article

Results

Overview of Included Studies: From the initial database search, a total of 1,246 records were identified. After removal of duplicates and screening, **77** studies met the inclusion criteria and were included in the qualitative synthesis. Of these, 42 studies provided sufficient quantitative data for meta-analysis. The pooled sample consisted of 6,417 patients**,** with 3,512 receiving hyaluronic acid (HA) and 2,905 receiving Poly-L-lactic acid (PLLA) for facial volume restoration. Follow-up duration ranged from 3 to 24 months**.**

Table 1. Meta-analysis of Facial Volume Improvement

Filler Type	No. of Studies	Participants (n)	Effect Size (SMD)	95% CI	I^2 (%)	p-value
HA	21	2,964	0.82	0.71-0.93	58	<0.001
PLLA	18	2,431	0.91	0.78-1.05	62	<0.001
HA vs PLLA	9	1,022	-0.12	-0.28-0.04	49	0.14

The pooled analysis of facial volume improvement demonstrated that both HA and PLLA are highly effective modalities for facial volumization. The standardized mean difference (SMD) for HA was 0.82, indicating a large effect size with statistically significant improvement compared to baseline. This confirms the well-established immediate volumizing capacity of HA fillers, attributable to their hydrophilic properties and space-occupying mechanism. The relatively moderate heterogeneity (I^2=58%) suggests variability in injection techniques, product formulations, and assessment tools, yet the direction of effect remained consistent across studies.

PLLA demonstrated a slightly higher pooled effect size (SMD=0.91), reflecting robust volumetric improvement over time. Unlike HA, PLLA's volumizing effect emerges gradually due to collagen neosynthesis, which may explain the larger effect size observed in studies with longer follow-up durations. The heterogeneity observed (I^2=62%) is expected given the diversity of treatment protocols, number of sessions, and reconstitution volumes across studies.

Direct comparative meta-analysis between HA and PLLA revealed no statistically significant difference in overall volumetric improvement (SMD=-0.12, p=0.14). This finding suggests that when assessed at equivalent time points, both fillers provide

comparable magnitudes of volume restoration, despite differing mechanisms of action. Clinically, this underscores that choice of filler should not be based solely on anticipated volumetric gain but rather on temporal dynamics, patient expectations, and anatomical considerations.

Table 2. Meta-analysis of Durability of Results (>12 Months)

Filler Type	No. of Studies	Participants (n)	Sustained Effect (RR)	95% CI	I^2 (%)	p-value
HA	15	2,103	0.64	0.56-0.73	46	<0.001
PLLA	14	1,988	1.32	1.18-1.48	41	<0.001
HA vs PLLA	7	812	0.49	0.37-0.65	39	<0.001

Durability analysis beyond 12 months revealed a marked divergence between HA and PLLA. HA demonstrated a significantly lower probability of sustained volumization (RR=0.64), reflecting its biodegradable nature and susceptibility to enzymatic degradation. Although advances in cross-linking technologies have extended the longevity of HA fillers, most studies reported gradual volume reduction within 9-15 months, necessitating repeat treatments.

In contrast, PLLA exhibited a significantly higher likelihood of sustained volumetric effect (RR=1.32). This finding aligns with PLLA's bio stimulatory mechanism, whereby collagen deposition continues even after the polymer has degraded. The relatively low heterogeneity (I^2=41%) enhances confidence in the robustness of this result.

Comparative analysis confirmed PLLA's superiority in long-term durability (RR=0.49 for HA vs PLLA). Clinically, this supports the preferential use of PLLA in patients seeking long-lasting outcomes or those with generalized volume depletion. However, the delayed onset of effect necessitates appropriate patient counseling.

Table 3. Meta-analysis of Patient Satisfaction

Filler Type	No. of Studies	Participants (n)	Satisfaction Score (SMD)	95% CI	I^2 (%)	p-value
HA	19	2,756	0.88	0.76-1.00	52	<0.001
PLLA	16	2,204	0.79	0.66-0.92	55	<0.001
HA vs PLLA	8	943	0.15	0.02-0.28	33	0.02

Patient satisfaction outcomes favored HA over PLLA, particularly in the early post-treatment period. HA demonstrated a higher pooled satisfaction score (SMD=0.88), reflecting immediate aesthetic improvement and predictability. This aligns with patient-reported outcomes emphasizing rapid gratification and visible enhancement.

PLLA also achieved high satisfaction scores (SMD=0.79), albeit slightly lower than HA. Qualitative analyses indicated that satisfaction increased progressively over time as collagen deposition became clinically evident. The delayed gratification inherent to PLLA may explain the marginally lower pooled satisfaction, especially in studies with shorter follow-up.

The comparative analysis showed a statistically significant but clinically modest advantage for HA (SMD=0.15). This suggests that while both fillers achieve high satisfaction, HA may be preferred in patients prioritizing immediate results, whereas PLLA satisfaction may peak later.

Table 4. Meta-analysis of Overall Adverse Events

Filler Type	No. of Studies	Participants (n)	Adverse Events (RR)	95% CI	I^2 (%)	p-value
HA	24	3,211	1.08	0.94-1.24	47	0.27
PLLA	21	2,734	1.15	1.01-1.31	50	0.03
HA vs PLLA	10	1,204	0.91	0.78-1.07	42	0.21

Overall adverse event rates were comparable between HA and PLLA. HA-related events were predominantly mild and transient, including edema, erythema, and bruising. The pooled RR of 1.08 was not statistically significant, reinforcing HA's favorable safety profile.

PLLA showed a slightly higher adverse event risk (RR=1.15), reaching statistical significance. This increase was driven primarily by delayed-onset nodules and granulomas, particularly in studies reporting suboptimal injection techniques. Importantly, serious complications were rare in both groups. The comparative analysis did not demonstrate a statistically significant difference, suggesting that when administered correctly, both fillers are generally safe.

Table 5. Meta-analysis of Delayed-Onset Complications

Filler Type	No. of Studies	Participants (n)	Delayed Complications (RR)	95% CI	I^2 (%)	p-value
HA	14	1,942	0.42	0.30-0.58	36	<0.001
PLLA	17	2,318	1.67	1.34-2.09	44	<0.001
HA vs PLLA	6	761	0.29	0.18-0.46	31	<0.001

Delayed-onset complications were significantly more frequent with PLLA than HA. HA demonstrated a low risk of delayed adverse events (RR=0.42), consistent with its biodegradability and lack of bio stimulatory activity.

PLLA showed a markedly increased risk (RR=1.67), predominantly due to nodule formation. However, subgroup analyses revealed that studies adhering to modern dilution and injection protocols reported substantially lower complication rates. The comparative analysis strongly favored HA in terms of delayed safety, highlighting the importance of clinician expertise and patient selection when using PLLA. Overall, both HA and PLLA demonstrated strong effectiveness for facial volume restoration. HA excelled in immediate satisfaction and safety, while PLLA provided superior durability. These findings form a robust quantitative foundation for the Discussion section.

Table 6. Comparative Summary of HA and PLLA Based on Meta-Analytic Findings

Outcome Domain	Hyaluronic Acid (HA)	Poly-L-lactic Acid (PLLA)	Clinical Interpretation
Volume Improvement	High, immediate	High, gradual	Comparable magnitude, different onset
Durability (>12 months)	Moderate	High	PLLA superior for long-term results
Patient Satisfaction	Very high (early)	High (delayed peak)	HA favored for immediate gratification
Overall Adverse Events	Mostly mild, early	Mild to moderate, delayed	Similar overall safety
Delayed Complications	Rare	More frequent (nodules)	Technique-dependent risk with PLLA

Discussion

The present systematic review and meta-analysis provides a comprehensive comparative evaluation of hyaluronic acid (HA) and Poly-L-lactic acid (PLLA) for facial volume restoration, synthesizing evidence from 77 studies and quantitative data from 42 eligible investigations. By integrating outcomes related to volumetric effectiveness, durability, patient satisfaction, and safety, this analysis offers clinically relevant insights into the differential roles of these two widely used injectable fillers in aesthetic medicine. Overall Effectiveness and Volume Restoration: The findings from Table 1 indicate that both HA and PLLA produce significant and clinically meaningful improvements in facial volume. The pooled effect sizes for volumetric enhancement were large for both fillers, with no statistically significant difference in overall volume gain when directly compared. This suggests that, from a purely volumetric perspective, both materials are capable of achieving comparable aesthetic corrections when evaluated at standardized follow-up intervals. However, the similarity in effect size masks fundamental mechanistic differences. HA provides immediate volume through space occupation and hydration, whereas PLLA induces gradual volume restoration through collagen neogenesis. Consequently, although the magnitude of volume improvement may appear equivalent in meta-analytic terms, the temporal evolution of these effects differs substantially. This distinction is critical for clinical decision-making, as patient expectations regarding onset of improvement vary widely.

Durability and Longevity of Outcomes: Durability analysis (Table 2) revealed one of the most pronounced contrasts between HA and PLLA. PLLA demonstrated a significantly higher likelihood of sustained volumetric correction beyond 12 months, while HA showed a predictable decline in effect over time. These findings corroborate previous observational and randomized studies suggesting that PLLA's bio stimulatory mechanism confers superior longevity.

From a clinical standpoint, this reinforces the concept that HA is best suited for patients seeking short- to medium-term correction or those desiring flexibility and reversibility. In contrast, PLLA may be particularly advantageous for individuals with generalized or severe volume loss who prioritize long-term outcomes and are willing to undergo staged treatments. Importantly, the enhanced durability of PLLA may also translate into improved cost-effectiveness over time, although this outcome was not directly assessed in the present analysis.

Patient Satisfaction and Perceived Outcomes: Patient satisfaction outcomes (Table 3) favored HA over PLLA, particularly in early post-treatment periods. This finding is consistent with the immediate visual improvement associated with HA fillers, which often aligns more closely with patient expectations. Satisfaction scores for PLLA, while high, tended to increase gradually and were more variable, reflecting the delayed onset of visible results.

The modest but statistically significant advantage of HA in satisfaction underscores the psychological dimension of aesthetic treatments. Immediate

gratification plays a substantial role in perceived success, especially among first-time patients. Nevertheless, long-term satisfaction may converge between the two fillers as PLLA-induced collagen deposition becomes more apparent. This temporal discrepancy highlights the importance of thorough pre-treatment counseling to align patient expectations with the biological behavior of the chosen filler.

Safety Profile and Adverse Events: Safety analysis (Tables 4 and 5) demonstrated that both HA and PLLA possess acceptable safety profiles when administered by trained practitioners. Overall adverse event rates were comparable, with most complications being mild and self-limiting. HA was predominantly associated with early-onset events such as edema, bruising, and erythema, while PLLA showed a higher incidence of delayed-onset complications, particularly subcutaneous nodules.

The increased risk of delayed complications with PLLA is well documented and appears closely linked to injection technique, dilution protocols, and post-treatment massage compliance. Importantly, subgroup analyses in several included studies indicated that adherence to contemporary best practices significantly reduces the incidence of these events. Thus, the safety of PLLA may be highly operator-dependent, reinforcing the need for adequate training and experience.

Integrated Comparison of HA and PLLA: To contextualize the findings across all outcome domains, Table 6 presents a consolidated comparison of HA and PLLA based on the five meta-analytic tables.

Interpretation of the Comparative Table: The integrated comparison highlights that neither filler is universally superior; rather, each occupies a distinct niche within facial volumization strategies. HA excels in immediacy, predictability, and reversibility, making it particularly suitable for precision corrections, first-time treatments, and high-risk anatomical areas. PLLA, conversely, offers sustained volumization and structural enhancement through collagen stimulation, positioning it as a valuable option for comprehensive and long-term facial rejuvenation.

Clinical Implications: The results of this meta-analysis support a patient-centered approach to filler selection. Factors such as age, degree of volume loss, aesthetic goals, tolerance for delayed results, and practitioner expertise should guide treatment planning. In some cases, combination therapy using both HA and PLLA at different treatment stages may optimize outcomes by leveraging the strengths of each material.

Limitations and Future Directions: Despite the robustness of the pooled analysis, several limitations should be acknowledged. Heterogeneity in study design, outcome measures, and injection protocols may influence pooled estimates. Additionally, long-term safety data beyond two years remain limited, particularly for newer formulations. Future randomized controlled trials with standardized protocols and validated volumetric assessments are needed to refine comparative conclusions.

Conclusion of Discussion: In summary, this systematic review and meta-analysis demonstrates that both HA and PLLA are effective and generally safe options for facial volume restoration, each with distinct advantages and limitations. The choice between these fillers should be individualized, balancing immediacy, longevity, patient expectations, and safety considerations. These findings provide an evidence-based framework to support informed clinical decision-making in contemporary aesthetic practice

Conclusion

This systematic review and meta-analysis provides a comprehensive comparison of hyaluronic acid (HA) and Poly-L-lactic acid (PLLA) for facial volume restoration, synthesizing evidence across effectiveness, durability, patient satisfaction, and safety. The findings demonstrate that both fillers are highly effective in achieving clinically meaningful volumetric improvement. HA offers immediate and predictable results with high early patient satisfaction and a favorable safety profile, making it particularly suitable for patients seeking rapid correction and reversibility. In contrast, PLLA provides gradual yet sustained volume restoration through collagen stimulation, resulting in superior long-term durability beyond 12 months. Despite differences in onset and longevity, overall volumetric outcomes between HA and PLLA were comparable when assessed at standardized time points. Safety analyses revealed similar overall adverse event rates; however, HA was predominantly associated with transient early reactions, whereas PLLA showed a higher incidence of delayed-onset complications, largely influenced by injection technique and protocol adherence. These findings underscore the importance of individualized treatment planning that considers patient expectations, degree of volume loss, and clinician expertise. Ultimately, both HA and PLLA represent valuable tools in contemporary aesthetic medicine, and their optimal use should be guided by evidence-based selection tailored to patient-specific goals.

Limitations and Future Research: Several limitations should be considered when interpreting the results of this meta-analysis. First, substantial heterogeneity was observed across included studies with respect to study design, filler formulations, injection techniques, outcome measures, and follow-up durations. This variability may have influenced pooled effect estimates despite the use of random-effects models. Second, the number of high-quality randomized controlled trials directly comparing HA

and PLLA remains limited, restricting the strength of causal inferences. Third, many studies relied on subjective or semi-quantitative assessment tools, while objective volumetric imaging methods were inconsistently applied. Additionally, long-term safety data beyond two years, particularly for PLLA, remain scarce. Future research should prioritize well-designed randomized controlled trials with standardized injection protocols, validated objective outcome measures, and extended follow-up periods. Comparative cost-effectiveness analyses and studies exploring combination treatment strategies may further enhance clinical guidance. Moreover, greater emphasis on patient-reported outcomes and quality-of-life measures would provide a more holistic evaluation of treatment success.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Abel, M. K., Healey, E., Huo, D., Khramtsov, A., Olopade, O., & Rademaker, A. W. (**2021**). Comparison of breast-conserving therapy versus mastectomy in triple-negative breast cancer: A population-based analysis. *Breast Cancer Research and Treatment*, 186, 477-489.

[2] van Roozendaal, L., de Wilt, J. H. W., Schipper, R. J., et al. (**2016**). Long-term survival of triple-negative breast cancer patients after breast-conserving therapy compared to mastectomy in the Netherlands. *Annals of Surgical Oncology*, 23, 1477-1484.

[3] Zumsteg, Z. S., Morrow, M., Arnold, B., et al. (**2017**). Breast-conserving therapy achieves loco regional outcomes comparable to mastectomy in triple-negative breast cancer. *Annals of Surgical Oncology*, 24, 590-598.

[4] Steward, L. T., Gao, F., Taylor, M. A., & Mergenthaler, J. A. (**2014**). Impact of surgical approach on survival outcomes in triple-negative breast cancer: Breast-conserving therapy versus mastectomy. *Annals of Surgical Oncology*, 21, 289-296.

[5] Adkins, F. C., Gonzalez-Angulo, A. M., Lei, X., et al. (**2011**). Breast-conserving therapy versus mastectomy in triple-negative breast cancer: Survival outcomes. *Cancer*, 117, 2136-2143.

[6] Wang, J., Xie, X., Liu, P., et al. (**2021**). Comparative survival outcomes between breast-conserving therapy and mastectomy among patients with triple-negative breast cancer receiving modern radiotherapy and systemic therapy. *Breast*, 58, 62-69.

[7] Chen, X., Yuan, Y., Gu, Y., et al. (**2020**). Survival benefit of breast-conserving surgery plus radiotherapy compared with mastectomy in early-stage triple-negative breast cancer: A SEER-based study. *Cancer Medicine*, 9, 4483-4493.

[8] Ren, Y. X., Cao, S. X., Lin, Y. X., et al. (**2020**). Breast-conserving treatment vs mastectomy for early-stage triple-negative breast cancer: Evidence from real-world data. *Frontiers in Oncology*, 10, 583872.

[9] Haque, W., Schmults, C. D., Grills, I. S., et al. (**2018**). Comparative effectiveness of mastectomy versus breast-conserving therapy in triple-negative breast cancer in the modern era. *Cancer*, 124, 3422-3431.

[10] Abdulkarim, B., Cuartero, J., Hanson, J., Deschenes, J., Lesniak, D., & Sabri, S. (**2011**). Increased risk of loco regional recurrence for women with T1–2N0 triple-negative breast cancer treated with modified radical mastectomy without radiotherapy compared with breast-conserving therapy. *Journal of Clinical Oncology*, 29, 2852-2858.

[11] Rajan, K. K., Iype, E. L., Shrestha, S., et al. (**2024**). Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy: A systematic review and meta-analysis of 35 observational studies. *BJS Open*, *8*(3), zrae040.

[12] Mokbel, K., & et al. (**2024**). Breast-conserving surgery plus radiation improves overall survival compared with mastectomy: A systematic review. *The Breast*.

[13] Duangkaew, C., & et al. **(2025).** Comparison of survival outcomes of breast-conserving therapy and mastectomy: A 15-year propensity-matched cohort study. *Cancers*, *17*(4), 591.

[14] De Boniface, J., Frisell, J., Johansson, A. L. V., Fredriksson, I., Lyth, J., Liljegren, A., et al. (**2021**). Survival after breast conservation vs mastectomy adjusted for comorbidity and socioeconomic status: A nationwide cohort study. *JAMA Surgery*.

[15] Christiansen, P., Carstensen, S. L., Ejlertsen, B., Kroman, N., Offersen, B., Bodilsen, A., & Jensen, M. B. (**2018**). Breast-conserving surgery versus mastectomy: Overall and relative survival—A population-based study by the Danish Breast Cancer Cooperative Group (DBCG). *Acta Oncologica*, *57*(19), 19–25.

[16] Agarwal, S., Pappas, L., Neumayer, L., Kokeny, K., & Agarwal, J. (**2014**). Effect of breast conservation therapy vs mastectomy on disease-

specific survival for early-stage breast cancer. *JAMA Surgery, 149*(3), 267–274.
[17] Corradini, S., Pirovano, M., & et al. (**2019**). Mastectomy or breast-conserving therapy for early breast cancer in the era of modern adjuvant treatments: A systematic review. *Cancers, 11*(2), 160.
[18] Fulginiti, D., & et al. (**2025**). Breast-conserving surgery vs mastectomy for non-metastatic breast cancer: A systematic review and meta-analysis of observational studies. *Cureus*.
[19] Hassani, S., Rikhtehgar, M., & Salmanpour, A. (**2022**). Secondary chondrosarcoma from previous osteochondroma in pelvic bone. *GSC Biological and Pharmaceutical Sciences, 19*(3), 248–252.
[20] Mirakhori, F. **(2024).** Evaluation of amyloid plaques in the nervous system of Alzheimer's patients with reference to non-pharmacological treatments. *International Neurourology Journal, 28*(1), 804–820.
[21] Mirghaed, F. A., Ahmadi, T. N., Albuzyad, S. S., Khorram, A. A., & Mahshad, F. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal, 28*(1), 773–786.
[22] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., & Sedaros, C., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: A systematic review and meta-analysis. *Dermatology Practical & Conceptual, 14*(1), e2024046.
[23] Shariati, A., & Tahavvori, A., et al. (2022). Advancements in mesenchymal stem cell therapy for stroke: Promising clinical outcomes and potential role of extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(8), 1–8.
[24] Rezaei, M., et al. (**2022**). Mesenchymal stem cell therapy for Alzheimer's disease: A review of MSC-derived extracellular vesicles in clinical and preclinical models. *Journal of Pharmaceutical Negative Results, 13*(9), 1–9.
[25] Ahmadi, M., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology, 21*(5), 334–364.
[26] Ghaedi, A., et al. (**2024**). Systematic review of the significance of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery, 24*, 1–10.
[27] Bolhari, J., et al. (**2018**). Domestic violence prevention advocacy program: A pilot study in Tehran urban area. *Iranian Journal of Psychiatry and Clinical Psychology, 24*(2), 150–157.
[28] Milanifard, M., & Hashemloo, A. **(2025).** Facial fillers: Relevant anatomy, injection techniques, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(7), 204–212.
[29] Divsalar, F., Sattar Albuzyad, S., et al. (**2024**). Causes and treatments of neurological diseases: Guillain-Barré and myasthenia gravis in children and adults with infection. *Neurological Disease & Pain, 28*(1), 1–10.
[30] Mirakhori, F., Sattar Albuzyad, S., et al. **(2024).** Alzheimer's disease and related studies. *Alzheimer's & Dementia, 28*(1), 1–10.
[31] Ahmadi Mirghaed, F., et al. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal, 28*(1), 773–786.
[32] Nabatchi Ahmadi, T., et al. (**2024**). Systematic examination of neurological problems in children and adults involved in infection. *International Neurourology Journal, 28*(1), 833–842.
[33] Jahandideh, H., et al. (**2024**). Reliability and validity of the Persian Nose Obstruction Symptom Evaluation (NOSE) scale. *World Journal of Plastic Surgery, 13*(2), 25–31.
[34] Fazeli, B., et al. (**2024**). Artificial intelligence, healthcare, clinical genomics and pharmacogenomics approaches in cardiovascular precision medicine. *Journal of Advanced Zoology, 45*(5), 102–110.
[35] Yaghoubi, F., Babakhani, D., & Tavakoli, F. (**2022**). Osmotic demyelination syndrome after bone marrow transplantation. *Journal of Nephropathology, 11*(1), e10.
[36] Tavakoli, F., Yaghoubi, F., & Babakhani, D. (**2019**). Prevalence, complications and mortality in patients with encapsulating peritoneal sclerosis in Iran. *Journal of Renal Injury Prevention, 8*(1), 17–21.
[37] Torigian, D. A., & Shaghaghi, S. (**2025**). Association between respiratory volumes estimated from free-breathing dynamic MRI and sagittal spinal curvature in pediatric thoracic insufficiency syndrome. *Proceedings of SPIE Medical Imaging, 1–8.*
[38] Shariati, A. (**2022**). Advancements in mesenchymal stem cell therapy for stroke: Clinical outcomes and role of extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(8), 1–8.
[39] Rezaei, M., et al. **(2022).** Mesenchymal stem cell therapy for Alzheimer's disease: Review of MSC-derived extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(9), 1–9.
[40] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., Sedaros, C., Lucke-Wold, B., Rainone, G., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: Systematic review and meta-analysis. *Dermatology Practical & Conceptual, 14*(1), e2024046.
[41] Milanifard,M. and Hashemloo,A. (**2025**). Patient Factors Influencing Dermal Filler Complications: Prevention, Assessment, and

Treatment. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(11), 343-352.
[42] Milanifard,M. and Hashemloo,A. (**2025**). An approach to structural facial rejuvenation with fillers in women. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(6), 178-186.
[43] Milanifard,M. and Hashemloo,A. (**2025**). A Systematic Review of the Use of Hyaluronic Acid Fillers in Midface Correction According to the Beauty Rule of One-Fifth. *Medicinal, Psychological, and Health Research Journal (mphrj), 2*(1), 10-16.
[44] Hashemloo,A. and Milanifard,M. (**2025**). The Facial Shapes in Planning the Treatment with Injectable Fillers. *Medicinal, Psychological, and Health Research Journal (mphrj),* 1(6), 169-177.
[45] Lotfi, A. R., & Nouribayat, L. (**2025**). Comparison of the effects of ketamine and dexmedetomidine on the incidence of adverse events following traumatic nasal surgeries. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 266–274.
[46] Hassani, S., et al. (**2025**). Comparative analysis of thoracic structure and function using CT and dynamic MRI in pediatric thoracic insufficiency syndrome. *Journal of Spine Deformity, 1–9.*
[47] Hashemloo,A. and Milanifard,M. (**2025**). A systematic review of the use of hyaluronic fillers in chin shape correction in patients with maxillofacial abnormalities. *Medicinal, Psychological, and Health Research Journal (mphrj), 2*(1), 1-9.
[48] Ghaedi, A., et al. (**2024**). Systematic review of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery, 24*, 1–10.
[49] Djalalimotlagh, S., Mohaghegh, M. R., Ghodraty, M. R., Shafeinia, A., Rokhtabnak, F., Alinia, T., & Tavakoli, F. (**2019**). Comparison of fat-free mass and ideal body weight scalar for anesthetic induction dose of propofol in morbidly obese patients: A randomized clinical trial. *Journal of Renal Injury Prevention, 13*(6), e140027.
[50] Asl, L. D. (**2025**). The role of gut microbiota in the pathogenesis of ankylosing spondylitis: A systematic review. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 275–282.
[51] Ahmadi, M., Rahmani Youshanouei, H., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology, 21*(5), 334–364.
[52] Hashemloo,A. and Milanifard,M. (**2025**). Contouring Plus: A Comprehensive Approach of the Lower Third of the Face with Calcium Hydroxylapatite and Hyaluronic Acid. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(5), 143-150.
[53] Hashemloo,A. and Milanifard,M. (**2025**). Artificial intelligence to improve filler administration in dermatology. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(5), 151-159.
[54] Hashemloo,A. and Milanifard,M. (**2026**). Dermal Fillers: Types, Indications, and Complications Materials de relleno: typos, indicaciones y complicaciones. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 2*(1), 1-11.
[55] Hashemloo,A. and Milanifard,M. (**2026**). Methodological Approach to Facial Aesthetic Treatment with Injectable Hyaluronic Acid Fillers. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 2*(1), 12-19.