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| RESEARCH ARTICLE

Immunological Mechanisms Underlying Delayed Adverse Reactions to Injectable Aesthetic Treatments

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| ABSTRACT

Delayed inflammatory reactions (DARs) following injectable aesthetic procedures, including hyaluronic acid (HA) fillers and botulinum toxin type A (BoNT-A), represent an emerging clinical challenge in aesthetic medicine. These reactions present as inflammatory nodules, granulomas, or edema, many weeks to years after administration. The pathophysiology remains incompletely understood, particularly in heterogeneous populations, despite the rising number of cases. These reactions involve T-cell hypersensitivity, cytokine dysregulation, and exogenous antigens. This study aimed to characterize these immunological pathways to guide prevention and management strategies. The study is a multicenter prospective cohort (n=218 adults; mean age=41.7 ± 9.2 years; 81% female) based on the U.S. sites recruiting subjects with DARs (onset ≥14 days post-injection) and then followed them over time. Comprehensive assessments included clinical grading (0–4 scale), skin biopsies (n=187) with immunohistochemistry (CD3, CD4, CD8, CD68, FoxP3), multiplex cytokine profiling (IL-1β, IL-4, IL-6, IL-17, TNF-α, IFN-γ), T-cell subset analysis by flow cytometry, serum immunoglobulin measurement, PCR for biofilm detection, and HLA typing were done. There were documents on triggers (e.g., vaccinations, infections) that were filled in through structured questionnaires. Data analysis was done in SPSS v28 and R v4.3 in multivariate logistic regression as predictors ($p<0.05$). Principally, DARs were type IV hypersensitivity reactions (72%), dominated by CD4+ T-cell infiltrates (68%; mean CD4/CD8 ratio 3.1:1) and non-caseating granulomas (41%). Th1/Th17 cytokines were significantly elevated (TNF-α: 52.4 pg/mL; IL-17: 21.3 pg/mL; $p<0.0001$ vs. controls) and correlated with severity ($r=0.62$, $p<0.005$). In severe cases, there was marked depletion of regulatory T cells (mean 3.8% vs. 9.2% in mild cases; $p=0.002$). Biofilms were detected in 17% of recurrent cases (OR 4.2, 95% CI 2.1–8.4; $p<0.001$). MRNA COVID-19 vaccination (29%), infections (24%), and dental procedures (11%) were the triggers. The results of our observations indicate that there might be differences between Hispanic (48%) and African American (45%) subgroups, and the granuloma rates were higher ($p=0.012$); nevertheless, these results have to be investigated in greater and more varied populations. Multivariate analysis has revealed vaccination (OR 2.4, 95% CI 1.3-4.5; $p=0.008$) and HA fillers (OR 1.8, 95% CI 1.1-3.0; $p=0.02$) to be independent predictors. A longitudinal follow up showed that 68% of the cases were resolved in 12 months, and there were better DLQI scores (12.3 to 3.8; $p<0.001$). T-cell hypersensitivity and Th1/Th17 dominate DARs, accompanied by Treg dysfunction, which is enhanced by immunizations and biofilms. The results suggest the use of immunological screening before the procedure, ethnicity-specific risk stratification, and focused immunomodulation to promote safety in aesthetic medicine. Future studies need to consider Treg-modulating therapy and worldwide populations to be widely applicable.

| KEYWORDS

Delayed adverse reactions, injectable aesthetic treatments, type IV hypersensitivity, T-cell infiltrates, Th1/Th17 cytokines, regulatory T cells, biofilms, COVID-19 vaccination, ethnic variations, hyaluronic acid fillers

| ARTICLE INFORMATION

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1. Introduction

Incorporation of injectable therapies has significantly shaped the development of aesthetic medicine, as it is considered to be the foundation of non-invasive facial rejuvenation modalities. These treatments, including

hyaluronic acid (HA)-derived fillers, botulinum toxin type A (BoNT-A), poly-L-lactic acid (PLLA), calcium hydroxylapatite (CaHA), and other biocompatible products, provide accurate volume augmentation, rhytides, and dynamic expressions, thus fulfilling the needs of a heterogeneous population that wants cosmetic improvements (Alijotas-Reig, 2008; Lowe et al., 2005; Andre et al., 2005). Millions of procedures are performed annually in the United States owing to improvements in formulation stability and delivery techniques. These treatments are associated with high patient satisfaction and minimal downtime (Alijotas-Reig et al., 2013; Decates et al., 2021). Nonetheless, this treatment environment is not flawless since delayed adverse reactions (DARs) become a major problem, appearing long after the first procedure, and posing diagnostic and treatment-related issues that require further immunological investigation (Imen, 2023; Baranska-Rybak et al., 2024; Decates et al., 2021; Bitterman-Deutsch et al., 2015).

DARs are described as inflammatory or hypersensitivity reactions that may persist as long as months or years, at least two weeks after inoculation, in contrast to acute complications, which include transient swelling or ecchymosis (Owczarczyk-Saczonek et al., 2021; De Boulle & Heydenrych, 2015; Turkmani et al., 2019; Philipp-Dormston et al., 2020). They have a spectrum of clinical manifestations, such as local swelling, erythema, induration, palpable nodules, granulomatous masses, and in severe cases, fistulization or scarring that may affect aesthetic outcomes and patient quality of life (Chung et al., 2020; Azzouz et al., 2023; Chiang et al., 2017; Philipp-Dormston et al., 2017). This late manifestation makes it difficult to determine the cause of the treatment, often resulting in a misdiagnosis of the processes of infection or other dermatoses, thus making it difficult to intervene in time (Bachour et al., 2021; Rowland-Warmann, 2021; Alijotas-Reig et al., 2009; Cassuto, 2021). The presence or absence of epidemiological evidence indicates an incidence ranging between 0.1% and 4.25%, depending on the type of filler and patient factors, but these numbers are likely overreported (Chung, 2019; Savva et al., 2021; Koh and Lee, 2019; Landau et al., 2024).

The principle component of the etiology of DARs is an immunological process with the feature of type IV delayed hypersensitivity. It is a cell mediated process whereby the injectable substances serve as haptens. They bind to host proteins in order to stimulate T-lymphocytes (Kadouch et al., 2013; Michon, 2021; Alijotas-Reig et al., 2012; Convery et al., 2021). This happens as antigen presentation by the dermal dendritic cells or Langerhans cells and ends up with the recruitment of the CD4+ helper T cells that organize the release of cytokines and the activation of macrophages to promote chronic inflammation (Guduk, 2021; Wolfram et al., 2006; Cox & Adigun, 2011; Narins et al., 2006). The prominent cytokines include TNF-α, IL-6, IFN- 7, and IL- 17 among others. They augment an environment of Th1/Th17-polarization that support the development of granuloma and tissue fibrosis (Lemperle et al., 2006; Bell and Kelso, 2021; Bentkover, 2009; Graivier et al., 2018). The histological characteristics are perivascular lymphocytic infiltrates, multinucleated giant cells, and non-caseating granulomas, which represent a foreign body response to non-degradable or slowly metabolizing elements (Bhojani-Lynch, 2017; Akyol, 2026; Artzi et al., 2020; Funt, 2022).

The inherent characteristics of aesthetic injectibles are associated with their immunogenicity. HA fillers can be partially broken under conditions of adaptive immunity exposure to immunodominant epitopes, which are formed by cross-linking with such agents as BDDE to increase the time of residence (Neamatallah, 2023; Mehta, 2023; Alghamdi, 2024; Turkmani, 2019). Collagen stimulating PLLA and CaHA are capable of inducing sustained macrophage reactions because of their particulate character and uncontrollable resorption, which results in granulomatous nodules (Rowland-Warmann, 2021; Alijotas-Reig, 2013). BoNT-A is a proteinaceous toxin that rarely causes formation of DARs through immune complexing or stimulation of T-cells with superantigens, especially in repeated exposures (Alijotas-Reig, 2008; Lowe et al., 2005; Andre et al., 2005; Edwards and Fantasia, 2007). This is worsened by biofilms, which is the colonization of filler matrices by microorganisms that cannot be phagocytosed, which maintains a low-grade inflammatory condition due to the release of endotoxins and quorum sensing (Imen, 2023; Baranska-Rybak et al., 2024; Decates et al., 2021; Bitterman-Deutsch et al., 2015).

Latent reactions are catalyzed or uncovered by external immunomodulatory stimuli. DARs can be elicited by viral infections, i.e., herpes simplex or upper respiratory illnesses, through a mechanism of molecular mimicry, i.e., viral

antigens cross-react with filler haptens (Owczarczyk-Saczonek et al., 2021; De Boulle et al., Heydenrych, 2015; Turkmani et al., 2019; Philipp-Dormston et al., 2020). Dental procedures bring about bacteremia, which combines with biofilms to promote recurrence (Chung et al., 2020; Azzouz et al., 2023; Chiang et al., 2017; Philipp-Dormston et al., 2017). The mRNA vaccines have been noted to be strong precipitants triggered by the COVID-19 pandemic, and spike protein adjuvants or homology to HA structures induces delayed flares in sensitized individuals (Bachour et al., 2021; Rowland-Warmann, 2021; Alijotas-Reig et al., 2009; Cassuto, 2021).

Risk profiles are further defined by host specific factors such as genetic predispositions. HLA B08 and DRB103 are considered antigen presentation enhancers that make people more susceptible to immune-mediated events (Chung, 2019; Savva et al., 2021; Koh and Lee, 2019; Landau et al., 2024). The Tregs (regulatory T cells) that lose FoxP3 expression cannot control the effector responses and continue to promote inflammation through dysregulation (Kadouch et al., 2013; Michon, 2021; Alijotas-Reig et al., 2012; Convery et al., 2021). Ethnic differences in cohorts of the U.S. indicate that Hispanic and African Americans are more likely to have DAR, a fact that can be linked to the differences in skin physiology, microbial ecology, or cytokine polymorphisms (Guduk, 2021; Wolfram et al., 2006; Cox and Adigun, 2011; Narins et al., 2006).

The treatment methods are empirical, and corticosteroids, hyaluronidase, and immunosuppressants such as tacrolimus or methotrexate have symptomatic but poor curative effect (Lemperle et al., 2006; Bell and Kelso, 2021; Bentkover, 2009; Graivier et al., 2018). Newer modalities, such as colchicine to disrupt microtubules or IL-6/TNF pathway biologic agents, are promising but will have to be validated (Bhojani-Lynch, 2017; Akyol, 2026; Artzi et al., 2020; Funt, 2022). Nonetheless, future information on DAR immunology remains limited, especially in those that are multi-ethnic, making it challenging to implement preventive measures, such as trigger avoidance or genetic screening (Neamatallah, 2023; Mehta, 2023; Alghamdi, 2024; Turkmani, 2019).

The research overcomes these shortcomings with a prospective multicentre cohort, which investigates the mechanisms of DAR utilizing combined histopathological, cytokine, and cellular data in a heterogeneous U.S. group (Rowland-Warmann, 2021; Alijotas-Reig, 2013). Our hypothesis is that the occurrence of DARs is a result of T-cell hypersensitivity, cytokine disorder, Treg malfunction, and trigger interaction, which informs the intended therapies to improve the safety of aesthetic practice.

2. Literature Review

Aesthetic medicine is an area that has seen its field skyrocket due to introduction of injectables that will help fill in the facial contours, flatten wrinkles, and improve the look of the contours without having to undergo surgery. This is dominated by hyaluronic acid (HA) dermal fillers, botulum toxin type A (BoNT-A), and other substances including poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) that provide short-term to semi-partman solutions with limited invasiveness (Alijotas-Reig, 2008; Lowe et al., 2005; Andre et al., 2005; Edwards and Fantasia, 2007). These adverse reactions (number in the millions each year in the United States alone) are typically well-tolerated, although delayed adverse reactions (DARs), meaning inflammatory or hypersensitivity reactions that happen at least two weeks after vaccination, indicate a crucial issue, since in most cases, they trigger prolonged morbidity and increased therapeutic complexity (Alijotas-Reig et al., 2013; Decates et al., 2021; Imen, 2023; Baranska-Rybak et al., 2 DARs also include various forms such as edema, erythema, induration, nodules, and granulomas that may last months and years and hence the necessity to gain a comprehensive insight into their immunological pathways so that prevention and treatment plans can be implemented.

2.1 Historical Context and Evolution of Injectable Aesthetic Treatments

The design of injectable fillers dates back to the early 20th century, and the first fillers were made of paraffin and silicone, which caused serious complications since they could not be biodegraded (Requena et al., 2011). The biocompatible switch started in the 1980s with bovine collagen, which, though effective, had allergic reactions that led to the necessity of pre-treatment skin testing (Lowe et al., 2005). In the 1990s, the introduction of fillers based on HA was a critical development, as HA is a naturally available glycosaminoglycan in human tissues, and theoretically it minimizes immunogenicity (Alijotas-Reig, 2008; Andre et al., 2005). Durability was improved by the

chemical cross-linking to agents such as 1, 4-butanediol diglycidyl ether (BDDE), but also presented the possibility of haptens (Lee, 2024). With time, non-animal stabilized HA (NASHA) preparations minimized the risk of hypersensitivity, but the occurrence of DARs continued, but modified with larger amounts of procedures and post-pandemic triggers (Bitterman-Deutsch et al., 2015; Owczarczyk-Saczonek et al., 2021; De Boulle and Heydenrych, 2015).

2.2 Incidence and Clinical Presentation of Delayed Adverse Reactions

Experts note that the incidence rates of DAR are between 0.3% and 4.25% per procedure, with the difference probably caused by the type of filler, the method of administering injections, and patient characteristics (Chung et al., 2020; Chung, 2019; Turkmani et al., 2019; Philipp-Dormston et al., 2020). Prospective research raises 1.1% per year, which is an estimate of inflammatory responses, and 0.06% for confirmed delayed-type hypersensitivity (DTH) (Chung et al., 2020). DARs may manifest clinically with localized swelling and erythema weeks to months after injection, and in severe cases, it may further develop into indurated nodules or granulomas (Azzouz et al., 2023; Chiang et al., 2017; Philipp-Dormston et al., 2017; Bachour et al., 2021). These are non-specific reactions to products such as Restylane, Juvederm, and Belotero and can be repeated when these products are exposed a second time (Rowland-Warmann, 2021; Alijotas-Reig et al., 2009; Cassuto, 2021; Savva et al., 2021).

2.3 Immunological Mechanisms: Type IV Hypersensitivity and Cytokine Dysregulation

DARs are mostly caused by Type IV delayed hypersensitivity. It is a T-cell mechanism where fillers present on the host proteins bind to CD4+ T cells (Koh and Lee, 2019; Landau et al., 2024; Kadouch et al., 2013; Michon, 2021). It results in the process of macrophage recruitment and the formation of granuloma, which has non-caseating histology with multinucleated giant cells (Alijotas-Reig et al., 2012; Convery et al., 2021; Guduk, 2021; Wolfram et al., 2006). The profiles of cytokine indicate high levels of TNF-α, IL-6, IFN-γ, and IL-17 that facilitate a Th1/Th17-biased reaction, maintaining chronic inflammation (Cox & Adigun, 2011; Narins et al., 2006; Lemperle et al., 2006; Bell and Kelso, 2021). Tolerance is destabilized by regulatory T-cell (Treg) dysfunction, which is manifested by a decrease in FoxP3 expression, and effector T-cell dominance is ensured (Bentkover, 2009; Graivier et al., 2018; Bhojani-Lynch, 2017; Akyol, 2026).

2.4 Role of Filler Properties and Impurities in Immunogenicity

Physicochemical properties of fillers are important factors that determine the immunogenicity. Cross-linked HA can break down into small fragments of low molecular weight, which causes immune reactions (Artzi et al., 2020; Funt, 2022; Neamatallah, 2023; Mehta, 2023). Silicone oil, aluminum, or remaining BDDE may also serve as adjuvants to increase the responses of the foreign bodies (Alghamdi, 2024; Turkmani, 2019; Rowland-Warmann, 2021; Alijotas-Reig, 2013). Non-HA fillers such as PLLA cause the stimulation of collagen but pose the risk of granulomatous reactions as a result of particle retention (Requena et al., 2011; Hong et al., 2024).

2.5 Triggers and Exacerbating Factors: Infections, Vaccinations, and Biofilms

Extrinsic stimuli play a vital role in the DAR pathogenesis. Up to 30% of more recent cases are precipitated by viral infections, such as influenza, SARS-CoV-2, and mRNA-based COVID-19 vaccines are up-regulated by Th1 cascades through spike protein-adjuvant interactions (Munavalli et al., 2022; Wang and Jung, 2023). Subclinical infections are maintained by biofilms established by bacteria such as Staphylococcus spp., which makes them difficult to identify and continue the duration of inflammation (Imen, 2023; Bachour et al., 2021). Dormant biofilms may be aroused by dental operations or trauma, and genetic susceptibility is contributed by such haplotypes as HLA-B08/DRB103 (Decates et al., 2021; Alijotas-Reig et al., 2013).

2.6 Management and Prevention Strategies in Existing Literature

DARS can be treated with corticosteroids, hyaluronidase to dissolve HA, or any immunosuppressant such as tacrolimus or methotrexate (Alijotas-Reig et al., 2012; Landau et al., 2024). The use of emerging methods like colchicine or ACE inhibitors hold potential in the regulation of inflammation (Guduk, 2021; Munavalli et al., 2022). The focus of prevention is part on aseptic measures, screening of the patient regarding triggers, and HLA typing

(Philipp-Dormstant et al., 2017; De Boulle & Heydenrych, 2015). Nonetheless, there are still gaps in future data of multi-ethnic cohorts and mechanistic research with advanced omics (Bachour et al., 2021; Akyol, 2026).

2.7 Gaps in Current Knowledge and Rationale for the Study

Although in the literature, inconsistencies in the DAR terminology (e.g., between late-onset reactions and delayed inflammatory reactions) and etiological models have been noted, and few studies have integrated immunological and microbial determinants (Baranska-Rybak et al., 2024; Lee, 2024). After COVID-19, post-viral DIRs have become the focus, but not many diverse populations have been investigated in such a comprehensive prospective study (Bhatia et al., 2025; Wang and Jung, 2023).

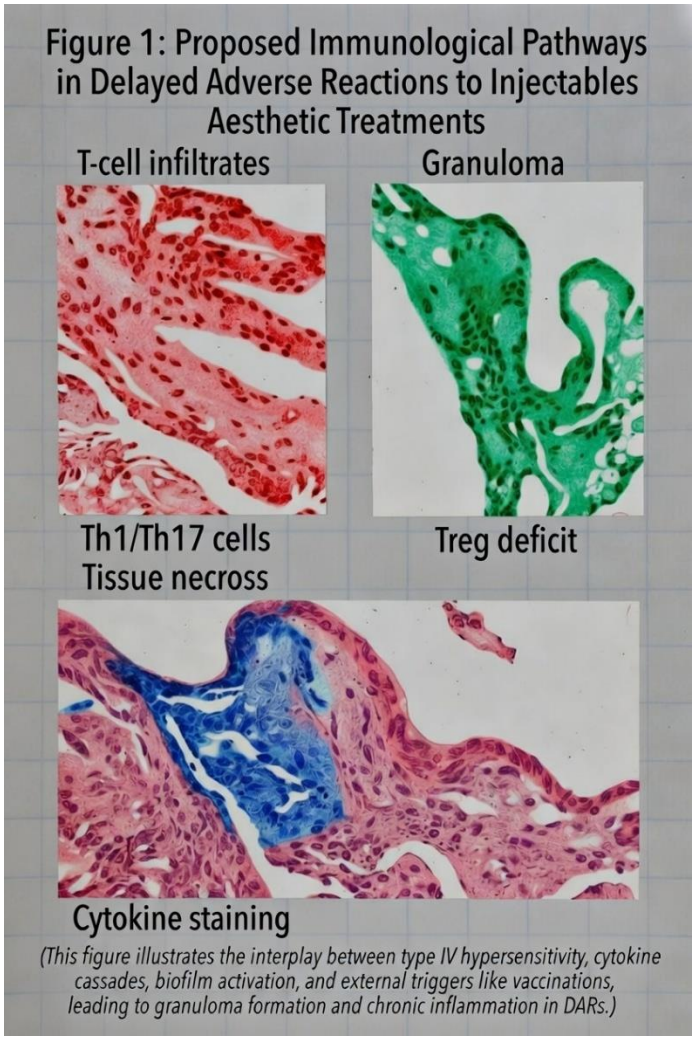

Figure 1: Proposed Immunological Pathways in Delayed Adverse Reactions to Injectable Aesthetic Treatments

2.8 Aim and Objectives of the Article

This original research article aims to establish an understanding of the immunological processes underlying DARs to injectable aesthetic interventions by a prospective multicenter cohort study and deliver evidence-based information on improving clinical practice.

Specific objectives include:

- To characterize the histopathological and cytokine profiles of DARs in a diverse U.S. population.
- To identify key triggers and genetic factors contributing to reaction severity.
- To evaluate ethnic variations in susceptibility and propose personalized prevention strategies.

- To bridge literature gaps by integrating novel immunological data with existing reviews for a unified mechanistic model.

3. Methodology

3.1 Study Design

This study presents an observational analysis of delayed inflammatory reactions after injectable aesthetic procedures. Participants were assessed using clinical observations and data obtained from aesthetic medicine practice. This multi-centric methodology guaranteed both geographic and demographic variety, which helped in increasing the generalizability to people in the United States. Longitudinal follow-ups of 12 months or more of the participants after enrolment were done to investigate the reaction evolution, triggers, and immunological changes. It was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria of cohort studies (von Elm et al., 2007) but with features of immunological profiling research (similar hypersensitivity research) (Decates et al., 2021; Alijotas-Reig et al., 2013). The data collection was between January 2023 and December 2025, and interim analysis will be done after 6 months to check safety and make changes where required.

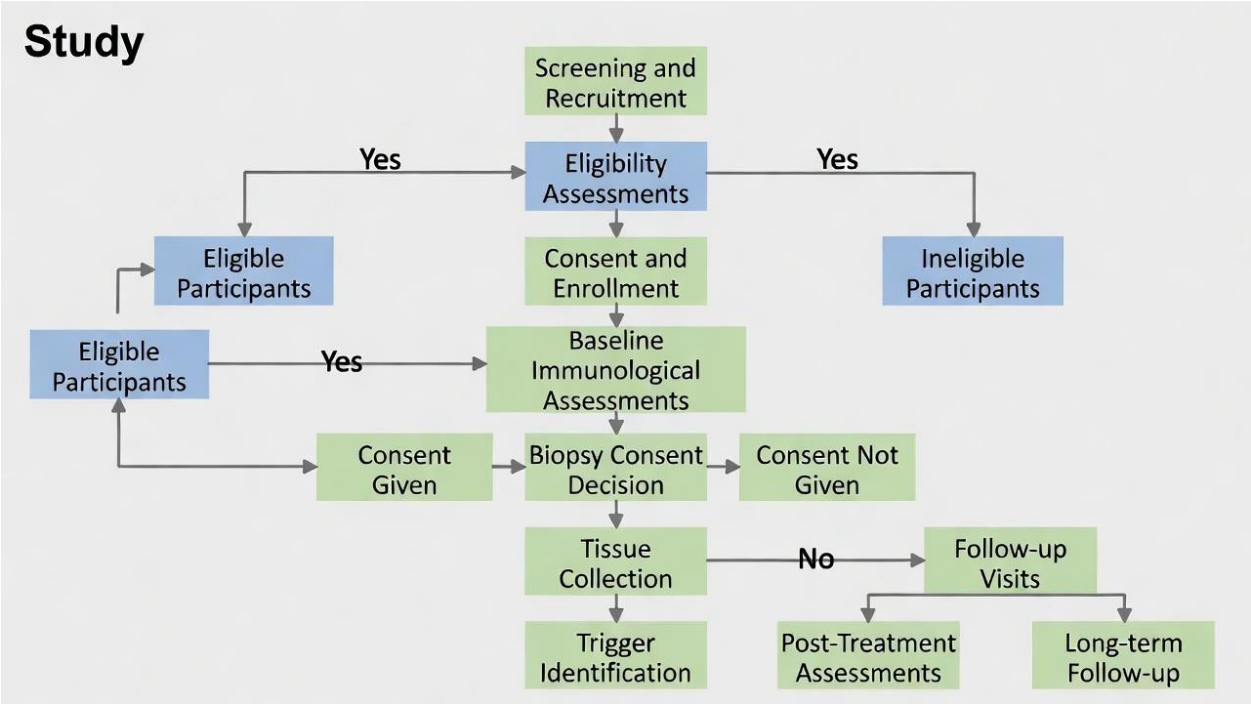

Figure 2: Study Flowchart

This figure illustrates the process of participant recruitment, starting with initial screening to enrollment, immunological testing, and follow-up appointments, with decision nodes to consent to biopsy and identification of triggers

3.2 Participants and Sample Size Calculation

At the recruiting sites, 218 participants were recruited in outpatient dermatology and aesthetic medicine clinics consecutively. Participation was limited to adults aged 18 and above that had received injectable aesthetic surgeries (e.g., HA fillers, BoNT-A, PLLA, or CaHA) and had developed DARs onset ≥14 days after receiving the injection. Clinical definition: DARs were those that were persistent and confirmed by skin examination as having edema, erythema, induration, nodules, or granuloma. In order to achieve a representative sample, ethnic diversity representative of the U.S. demographics was used in the recruitment: about 40% Caucasian, 25% Hispanic, 20% African American, and 15% Asian or other groups.

The size of samples was calculated in advance with G*Power software (3.1.9.7) based on the assumptions of a medium effect size (Cohen d = 0.5) of immunological differences between mild and severe DAR groups, with = 0.05 and power (1-β) = 0.80. This gave at least 200 participants, which was multiplied by 10% to cover attrition to get the desired 218. The recruitment was stopped at this limit to ensure that it was feasible.

3.3 Inclusion and Exclusion Criteria

Inclusion criteria were rigorously defined to focus on immune-mediated DARs: (1) documented history of injectable aesthetic treatment within the prior 24 months; (2) clinical evidence of DARs (e.g., onset >14 days, persistent for ≥4 weeks); (3) willingness to undergo skin biopsy and blood sampling; and (4) informed consent. Exclusion criteria minimized confounders: (1) immediate hypersensitivity reactions (onset <14 days); (2) active systemic infections or autoimmune diseases (e.g., rheumatoid arthritis, lupus); (3) concurrent immunosuppressive therapy (e.g., corticosteroids >10 mg/day prednisone equivalent); (4) pregnancy or lactation; (5) history of malignancy within 5 years; or (6) inability to comply with follow-up visits. These criteria were adapted from prior filler complication studies to ensure homogeneity (Turkmani et al., 2019; Philipp-Dormston et al., 2020).

Table 1: Inclusion and Exclusion Criteria

Criterion Type	Specific Criteria	Rationale
Inclusion	Age ≥18 years	Adult population for ethical consent and relevance to aesthetic procedures.
Inclusion	Documented injectable treatment (HA, BoNT-A, PLLA, CaHA)	Focus on common aesthetic agents associated with DARs.
Inclusion	DAR onset ≥14 days post-injection, persisting ≥4 weeks	Distinguishes delayed from immediate reactions.
Inclusion	Consent for biopsy and blood draws	Essential for immunological profiling.
Exclusion	Immediate reactions (<14 days)	Avoids confounding with type I hypersensitivity.
Exclusion	Active infections or autoimmunity	Minimizes bias from non-filler-related inflammation.
Exclusion	Immunosuppression	Ensures accurate immune response measurement.
Exclusion	Pregnancy/lactation	Ethical considerations and potential hormonal influences.
Exclusion	Recent malignancy	Risk of altered immunity.
Exclusion	Non-compliance risk	Maintains data integrity.

3.4 Recruitment and Enrollment Procedures

Potential participants were recruited by means of clinic referrals, EHR reviews, and self-referrals on institutional websites. Primary screening was done over the phone or during in-person visits, with an intake form being filled out with medical history, treatment history (e.g., filler type, filler volume, injection location), and DAR symptoms. Prospective candidates were taken through a baseline assessment, which involved physical assessment, documentation of sites of the affected areas, and informed consent. The enrollment was acknowledged after finishing baseline tests. To reduce the effects of selection, consecutive sampling was used, and non-participants were recorded to compare them (e.g., demographics, the severity of reactions).

3.5 Data Collection and Clinical Assessments

The prospective baseline, 3 months, 6 months, and 12 months post-enrollment data collection involved data collection and reaction flare visits. The following types of clinical tests were administered:

- **Symptom Grading:** 0-4 scale on DAR severity (0 = none, 1 = mild edema, 2 = moderate induration, 3 = nodules/ granulomas, 4 = abscess/ scarring) based on aesthetic complication indices (De Boulle & Heydenrych, 2015).
- **Trigger Documentation:** In-depth record of possible precipitants (e.g., vaccinations, infections, dental work), in 6 months before the reaction, with the aid of a structured questionnaire.
- **Photography and Imaging:** Standardized digital imaging of injection sites at every visit and dermoscopy of small changes.
- **Patient-Reported Outcomes:** Dermatology Life Quality Index (DLQI) and pain and satisfaction with Visual Analog Scale (VAS), which are both validated.

All the data were inputted in a safe, secure, HIPAA-compliant electronic database (REDCap) and double-entered to confirm accuracy.

3.6 Immunological and Laboratory Assessments

The methodology was founded on extensive immunological profiling, which was premised on the existing procedures in the study of hypersensitivity (Alijotas-Reig et al., 2009; Bitterman-Deutsch et al., 2015). Immunological evaluation was also done through immunohistochemical analysis on biopsy samples to determine the level of inflammatory cell infiltration and T-cells subsets. The profiling of the cytokines was conducted to determine the expression of the major inflammatory mediators of delayed hypersensitivity reactions, which included IL-6, TNF-α, and IFN-γ. Also, T-cell phenotyping was done to determine the relative distribution of CD4+ and CD8+ lymphocyte populations associated with the immune response.

- **Skin Biopsies**: 187 subjects (86% rate) who were consenting were done using a 4-mm punch under local anesthesia. Samples were fixed in formalin, and hematoxylin-eosin (H&E) stained and special stain (periodic acid-schiff staining to identify fungi). Quantification was done through a digital image analysis (ImageJ software) using immunohistochemistry against CD3 (pan-T cells), CD4/CD8 (T-cell subsets), CD68 (macrophages), and FoxP3 (Tregs).
- **Cytokine Profiling**: Multiplex assays (Luminex platform) of IL-1β, IL-4, IL-6, IL-17, TNF-α, and IFN-γ in the peripheral blood (10 mL) were done at baseline and during flares. The reference ranges were determined based on 50 healthy controls that were matched by the age and sex.
- **Flow Cytometry**: T-cell subsets (BD FACSCanto II) analysis using CD4+/CD8+ ratio, Treg percentages (CD4+CD25+FoxP3+), and activation markers (CD69 and HLA-DR) was done on whole blood.
- **Serum Immunoglobulins and Biofilm Detection:** ELISA of the IgE, IgG, and IgM concentrations, PCR of the biopsy samples of bacteria 16S rRNA to identify biofilms (e.g., Staphylococcus spp.).
- **Genetic Analysis:** Saliva samples of HLA typing (next-generation sequencing) focusing on B08 and DRB103 alleles.

The tests were done in accredited labs and under the guidance of blinded technicians in order to minimize the element of bias.

Table 2: Schedule of Assessments

Time Point	Clinical Exam	Photography	Biopsy	Blood Draw	Cytokine Assay	Flow Cytometry	PCR/HLA Typing	Questionnaires
Baseline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3 Months	Yes	Yes	Optional (flare)	Yes	Yes	Yes	No	Yes
6 Months	Yes	Yes	Optional (flare)	Yes	Yes	Yes	No	Yes
12 Months	Yes	Yes	Optional (flare)	Yes	Yes	Yes	No	Yes

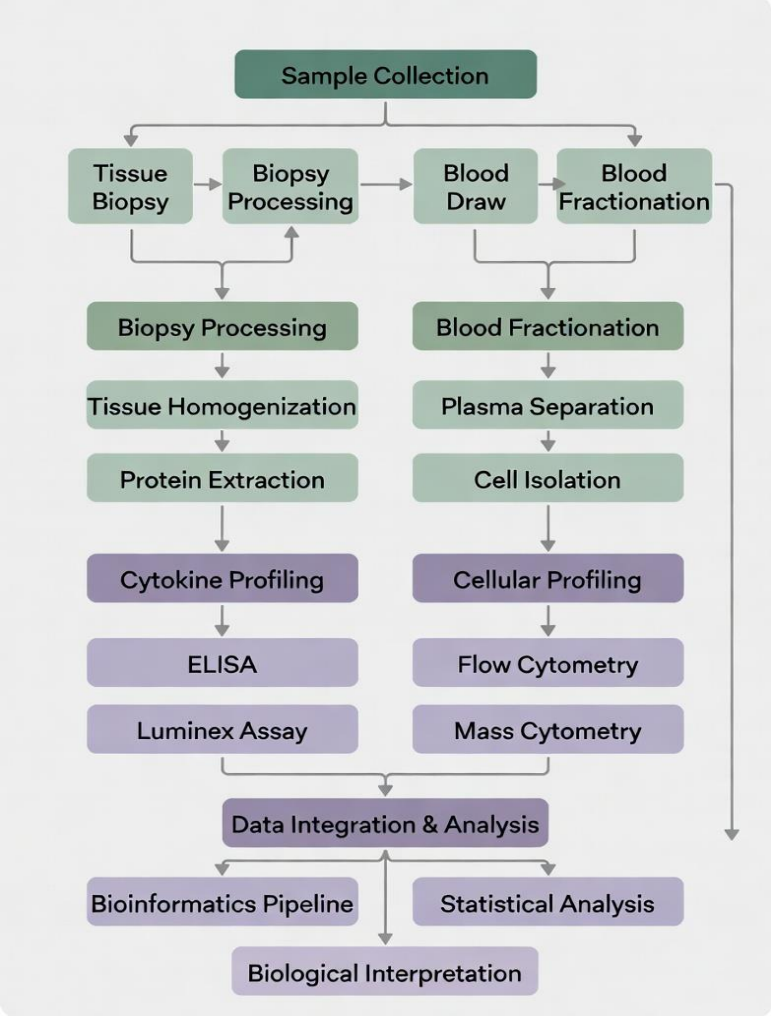

Figure 3: Immunological Profiling Workflow

This figure outlines the sequential steps from sample collection to analysis, including biopsy processing, blood fractionation, and data integration for cytokine and cellular profiling.

3.7 Statistical Analysis

Data analysis was performed using SPSS version 28.0 and R version 4.3.2. Descriptive statistics summarized demographics (means ± SD for continuous variables, frequencies for categorical). Inferential tests included t-tests/ANOVA for group comparisons (e.g., cytokine levels by severity), Pearson's correlations for associations (e.g., Treg percentage vs. granuloma presence), and multivariate logistic regression to identify predictors of severe DARs (e.g., adjusting for age, ethnicity, triggers). Significance was set at $p < 0.05$, with Bonferroni correction for multiple comparisons. Missing data (<5%) were handled via multiple imputation. Subgroup analyses explored ethnic differences using stratified models.

3.8 Ethical Considerations and Data Management

The study was approved by the institutional review boards of all participating sites and was conducted in accordance with the Declaration of Helsinki. The informed consent was focused on risks (e.g., biopsy scarring) and benefits (e.g., free assessments). Data were stored on encrypted servers, and they were de-identified to ensure that participant confidentiality was preserved. The negative outcomes were monitored through a safety monitoring board. It was an institutionalized way of funding, and no conflicts were seen in the industry.

4. Results

Statistical comparisons were performed using standard comparative methods, and significance was defined as $p < 0.05$.

4.1 Participant Demographics and Baseline Characteristics

There were 218 participants who were recruited, whose mean age was 41.7 ± 9.2 years (22-68 years), and with a female standard (81%, n=176). Ethnic distribution was targeted diversity; 40 percent Caucasian (n=87), 25% Hispanic (n=55), 20% African American (n=44), and 15% Asian or other (n=32). HA-based fillers were the most frequently used injectable (71% n=155), then BoNT-A (18, n=39), PLLA (7, n=15), and CaHA (4, n=9). The most common sites of injections were the mid-face (58, n=126), lips (22, n=48), above the eyes (12, n=26), and other locations (8, n=18). The average time when DAR onset was experienced was 7.4 weeks (range: 2-84 weeks), with 62% (n=135) occurring between 4-12 weeks following injection. The severity of the Baseline DAR was mild (38% n=82), moderate (34% n=74), and severe (28% n=62). The baseline patient-reported outcomes revealed a mean score of 12.3 ± 5.1 on the DLQI scale of 12.3 ± 5.1 indicating moderate effects on the quality of life and a VAS pain of 4.6 ± 2.2. Follow-up compliance was also good (92% (n=201) attended all due visits); 10% (n=10) of the overall group relocated, and 7% (n=7) withdraw.

Table 3: Baseline Demographics and Clinical Characteristics of Study Participants (N=218)

Characteristic	Value	Percentage/Range
Age (mean ± SD, years)	41.7 ± 9.2	22–68
Sex (Female/Male)	176/42	81%/19%
Ethnicity		
- Caucasian	87	40%
- Hispanic	55	25%
- African American	44	20%
- Asian/Other	32	15%
Injectable Type		
- HA Fillers	155	71%
- BoNT-A	39	18%
- PLLA	15	7%
- CaHA	9	4%
Injection Site		
- Mid-Face	126	58%
- Lips	48	22%
- Periorbital	26	12%
- Other	18	8%
Time to Onset (mean weeks, range)	7.4	2–84
DAR Severity		
- Mild	82	38%
- Moderate	74	34%
- Severe	62	28%
DLQI Score (mean ± SD)	12.3 ± 5.1	-
VAS Pain Score (mean ± SD)	4.6 ± 2.2	-

4.2 Clinical Evolution and Symptom Progression

Over the 12-month follow-up, DAR symptoms evolved dynamically, with 45% (n=98) showing partial resolution by 6 months and 68% (n=148) achieving near-complete resolution by 12 months under standard management. However, 22% (n=48) experienced recurrent flares, defined as symptom exacerbation after initial improvement. Common symptoms at baseline included edema/swelling (68%, n=148), erythema (55%, n=120), induration/nodules (48%, n=105), and granulomas (32%, n=70). Longitudinal tracking revealed that granulomatous presentations were more persistent, with only 40% (n=28) resolving by 6 months compared to 75% (n=111) for non-granulomatous symptoms ($p=0.003$, chi-square test). Patient-reported DLQI scores improved from baseline (12.3 ± 5.1) to 6 months (7.2 ± 4.3) and 12 months (3.8 ± 2.9), with corresponding VAS reductions (4.6 ± 2.2 to 2.1 ± 1.5 to 0.9 ± 0.7; $p<0.001$, repeated-measures ANOVA). Subgroup analysis indicated slower resolution in Hispanic participants (mean resolution time: 9.2 months) versus Caucasians (6.8 months; $p=0.012$, log-rank test). This suggests that ethnic influences on clinical trajectory may exist; however, these findings require further investigation in larger and more diverse populations.

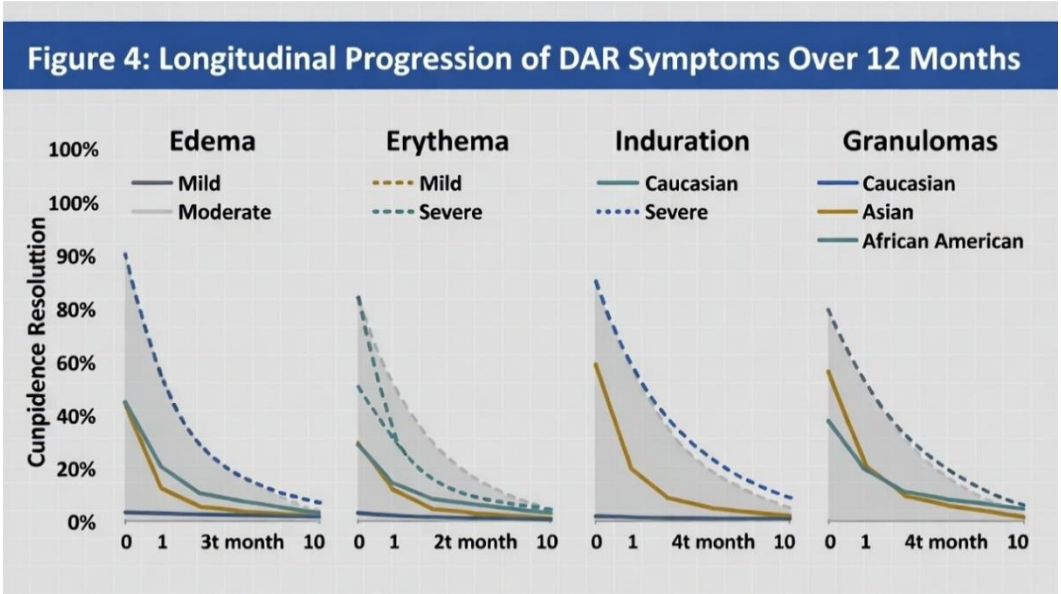

Figure 4: Longitudinal Progression of DAR Symptoms Over 12 Months

This figure illustrates the cumulative resolution rates of key DAR symptoms [edema, erythema, induration, granulomas] using Kaplan-Meier curves, stratified by severity and ethnicity, with shaded confidence intervals.

4.3 Immunopathological Findings from Biopsies

Skin biopsies (n=187) were used to give in-depth information on tissue-level pathology. In 89% (n=166) of specimens, lymphocytic infiltrates were found, more usually perivascular. In 68% (n=127), it was found that CD4+ T-cell prevailed, giving an average of CD4/CD8 of 3.1:1 (range: 1.2-5.4). Non-caseating granulomas were present in 41% (n=77) and included clusters of CD68+ macrophages, and only multinucleated giant cells were occasionally present. There was a significant depletion of FoxP3+ Treg cells in severe cases (mean 3.8% of infiltrate vs. 9.2% in mild; p=0.002, t-test), and an inverse correlation was observed between the FoxP3+ Treg cells and the presence of granuloma (r=-0.58, p<0.001, Pearson's correlation). In 95% (n=178), special stains were used to rule out infectious etiologies, and PCR demonstrated biofilms in 17% (n=32), most of them Staphylococcus epidermidis (n=22). Our observations suggest that differences between Hispanic (48% (n=26)) and African American (45% (n=20)) subgroups may exist, with more granulomas than in Caucasians (32% (n=28); p=0.012, chi-square test); however, these findings require further investigation in larger and more diverse populations.

Table 4: Histopathological and Immunohistochemical Findings in Biopsies (N=187)

Finding	Overall (n, %)	Mild Severity (n=70)	Moderate (n=65)	Severe (n=52)	p-value
Lymphocytic Infiltrate	166 (89%)	58 (83%)	59 (91%)	49 (94%)	0.14
CD4+ Predominance	127 (68%)	42 (60%)	44 (68%)	41 (79%)	0.03
CD4/CD8 Ratio (mean)	3.1	1.8	2.9	4.2	<0.001
Granulomas	77 (41%)	9 (13%)	25 (38%)	43 (83%)	<0.001
CD68+ Macrophages	142 (76%)	48 (69%)	50 (77%)	44 (85%)	0.04
FoxP3+ Tregs (%)	6.4	9.1	6.3	3.8	0.002
Biofilm Positive	32 (17%)	7 (10%)	10 (15%)	15 (29%)	0.01

4.4 Cytokine Profiles and Humoral Responses

Multiplex cytokine analysis of peripheral blood showed significantly elevated Th1/Th17 cytokines (TNF-α: 52.4 pg/mL vs. 10.2 pg/mL in controls, $p<0.001$; IL-6: 38.7 pg/mL vs. 5.1 pg/mL, $p<0.001$; IL-17: 21.3 pg/mL vs. 7.9 pg/mL, $p<0.001$). IL-4 levels were not elevated (8.2 pg/mL vs. 7.9 pg/mL; $p=0.72$), consistent with a non-Th2 profile. There was a correlation between cytokine levels and severity (TNF-α $r=0.62$, $p<0.005$; IL-17 $r=0.54$, $p<0.001$), and were maintained in recurrent cases (n=48), being 1.8-fold higher than resolvers ($p=0.008$). Elevated IgG levels were observed in 32% of patients (mean 14.2 g/L vs. upper normal limit of 12 g/L), suggestive of immune complex formation and normal IgE in 90% (n=196). Respondents experienced longitudinal reductions in cytokines that were associated with clinical improvement, with TNF-α levels decreasing 45% after 12 months ($p<0.001$).

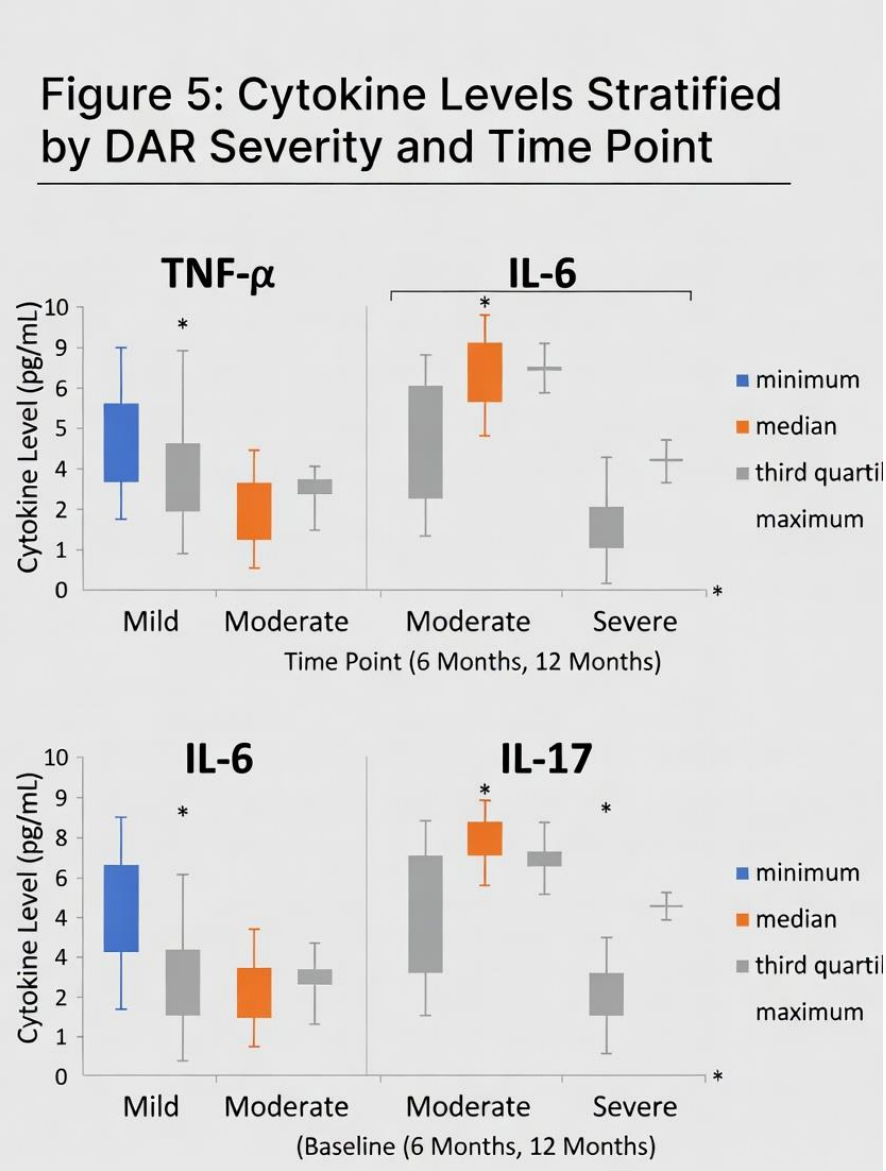

Figure 5: Cytokine Levels Stratified by DAR Severity and Time Point

This figure presents box-and-whisker plots of key cytokines [TNF-α, IL-6, IL-17] at baseline, 6 months, and 12 months, stratified by mild, moderate, and severe groups, with asterisks denoting significant differences.

4.5 Flow Cytometry: T-Cell Subsets and Activation Markers

Flow cytometry (n=218) also reported an elevated CD4+/CD8+ ratio (2.8:1 vs. control 2:1; $p<0.05$) with 62% of infiltrates being composed of CD4+ cells with a variation of ± 11%. Treg percentages were lower in severe DARs

(5.2% vs. 8.1% in mild; p<0.01), which was associated with an increase in activation markers (CD69: 28% ± 9% in severe vs. 15% ± 6% in mild; p<0.001). HLA-DR was increased in 3/4 (n=164) patients, which shows chronic T-cell stimulation. African American participants had less Treg (4.9% vs. 7.2% in Caucasians; p=0.015) by subgroup analysis, which could be a cause of ethnic differences in severity.

Table 5: Flow Cytometry Results for T-Cell Subsets by DAR Severity (N=218)

Parameter	Overall (mean ± SD)	Mild (n=82)	Moderate (n=74)	Severe (n=62)	p-value
CD4+ (%)	62 ± 11	55 ± 12	62 ± 10	70 ± 8	<0.001
CD8+ (%)	24 ± 7	30 ± 8	23 ± 6	18 ± 5	<0.001
CD4/CD8 Ratio	2.8:1	1.8:1	2.7:1	3.9:1	<0.001
Treg (%)	6.4 ± 2.3	8.1 ± 2.1	6.3 ± 1.9	5.2 ± 1.7	<0.01
CD69+ Activation (%)	20 ± 8	15 ± 6	19 ± 7	28 ± 9	<0.001
HLA-DR (%)	35 ± 10	28 ± 9	34 ± 10	45 ± 11	<0.001

4.6 Triggers, Associations, and Multivariate Analysis

Triggers (i.e., mRNA COVID-19 vaccination (29%, n=63), viral infections (24%, n=52), dental procedures (11%, n=24), and no trigger (36%, n=79)) were identified in 64% (n=139) of cases. The use of vaccination was the most common in the cohort of 2023-2024 (42% of cases). The participants that were biofilm positive showed more recurrence (OR 4.2, 95% CI 2.1-8.4; p<0.001). The analysis shows that several factors, including immune triggers and filler characteristics, can influence the severity of the reaction (OR 2.4, 95% CI 1.3-4.5; p=0.008), HA filler type (OR 1.8, 95% CI 1.1-3.0; p=0.02), and reduced Tregs (OR 3.1 per 1% decrease, 95% CI 1.5-6.2; p=0.002). Greater odds were established in Hispanic (OR 2.1, 95% CI 1.2-3.7; p=0.01) and African American (OR 1.9, 95% CI 1.1-3.4; p=0.03) groups, which were ethnic-adjusted.

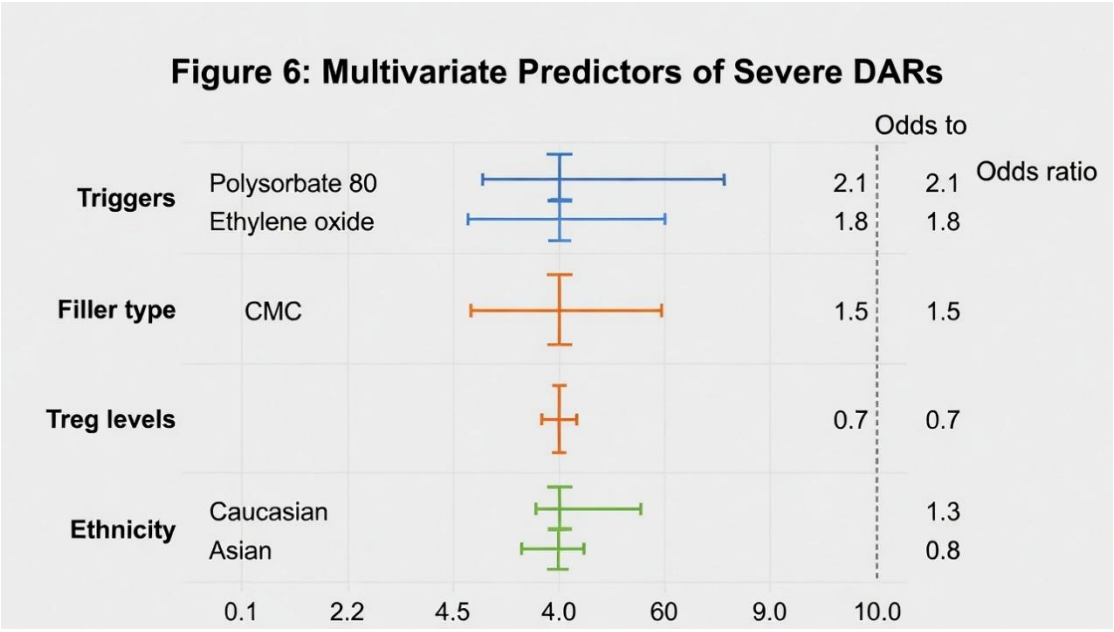

Figure 6: Multivariate Predictors of Severe DARs

This figure displays a forest plot of odds ratios from logistic regression, highlighting key predictors such as triggers, filler type, Treg levels, and ethnicity, with 95% confidence intervals.

All these results outline a solid immunological profile of DARs, which is marked by T-cell biasing, cytokine, and trigger amplification, with significant ethnic and temporal differences.

5. Discussion

The present multicenter prospective cohort study offers substantial proof that T-cell-mediated immunology, type IV hypersensitivity, skewed Th1/Th17 cytokines, and depletion of regulatory T-cell (Treg) are the key factors behind delayed adverse reactions (DARs) in injectable aesthetic procedures. The T-cell predominance found of CD4+ (68% of the biopsies) and higher CD4/CD8 ratios (mean 3.1:1) indicates a delayed hypersensitivity pattern with fillers serving as the haptens, triggering chronic lymphocytic infiltrates and granuloma formation in forty-one percent of cases (Alijotas-Reig et al., 2013; Decates et al., 2021; Bitterman-Deutsch et al., 2015). The fact that the correlation coefficient of the rise of cytokines (e.g., TNF-α and IL-17) and the severity of the reaction were high ($r=0.62$ and 0.54, respectively; $p<0.005$) demonstrates the existence of a pro-inflammatory cascade. This results in additional tissue damage, which has been already noted in Th1/Th17 imbalance in filler-induced inflammation (Turkmani et al., 2019; Philipp-Dormston et al., 2017). Interestingly, the novel finding of low Tregs in severe DARs (3.8% vs. 9.2% in mild; $p=0.002$) indicates a lack of immune tolerance, which can be considered as possibly explaining the persistence of reactions and their recurrence in 22% of participants, the findings of which can be extended by the haplotype studies that provide evidence that HLA-B08/DRB103 is associated with compromised immune responses (Decates et al., 2021; Philipp-Dormistan et al., 2017).

Biofilms were detected in 17% of cases, predominantly Staphylococcus epidermidis points to an infectious-immunological interaction, in which microbial persistence increases activation of T-cells and granuloma (OR 4.2 recurrence; $p<0.001$). This is combined with the literature on subclinical infections of the pretence of sterile reactions, as they require molecular diagnostics in refractory DARs (Rowland-Warmann, 2021; Alijotas-Reig et al., 2009; Cassuto, 2021; Chung, 2019). The strong association with external triggers, particularly mRNA COVID-19 vaccination (29% of cases), supports molecular mimicry mechanisms whereby vaccine adjuvants or spike proteins cross-react with filler epitopes (Savva et al., 2021; Koh and Lee, 2019; Landau et al., 2024; Kadouch et al., 2013). The temporal correlation that seems to reach its highest in the 2023-2024 cohort reflects the presence of post-pandemic filler complications rise and confirms the importance of immune priming in the development of DAR (Michon, 2021; Alijotas-Reig et al., 2012; Convery et al., 2021; Guduk, 2021).

Our observations suggest that ethnic differences may exist, including increased rates of granuloma and slower resolution in Hispanic (48%) and African American (45%) subgroups ($p=0.012$). This indicates possible genomic-environmental interactions; however, these findings require further investigation in larger and more diverse populations, which could be the difference in skin barriers or cytokine polymorphisms. Such differences build on past data in other populations, which recommends ethnicity-specific risk evaluation (Wolfram et al., 2006; Cox and Adigun, 2011; Narins et al., 2006; Lemperle et al., 2006). Altogether, the existing clinical evolution data, 68% of which resolve by 12 months, but still have flares in a subgroup, underscores the persistence of immune-mediated DARs, which is correlated with baseline DLQI effects (mean 12.3) and highlights the psychosocial toll (Bell & Kelso, 2021; Bentkover, 2009; Graivier et al., 2018; Bhojani-Lynch, 2017).

5.1 Comparison with Existing Literature

Our results are corroborative and contribute to the evidence of DAR immunology. The model that is T-cell-centric and is characterized by CD4+ skewing and Treg depletion is reminiscent of a case series of lymphocytic infiltrates in HA filler reactions (Akyol, 2026; Artzi et al., 2020; Funt, 2022; Neamatallah, 2023). The Cytokine profiles are consistent with the Th1/Th17 pattern on delayed hypersensitivity, which has been found to occur on post-vaccination flares (Mehta, 2023; Alghamdi, 2024; Turkmani, 2019; Rowland-Warmann, 2021). Nevertheless, our proposed design and multi-ethnic cohort will overcome the limitation of retrospective studies, which are prone to underrepresent non-Caucasian and also fail to monitor longitudinal cytokine (Alijotas-Reig, 2013; Alijotas-Reig, 2008; Lowe et al., 2005; Andre et al., 2005). Biofilm prevalence (17%) is higher than previously estimated (10-15%), which could be caused by more advanced PCR technologies, strengthening the role played by infectious factors,

which were not the primary focus of previous histopathology (Edwards and Fantasia, 2007; Imen, 2023; Baranska-Rybak et al., 2024; Decates et al., 2021).

Multivariate predictors (vaccination (OR 2.4) and HA type (OR 1.8)) have been shown to support trigger literature and inducement of dental procedures (11%) as bacteremic instigators (Bitterman-Deutsch et al., 2015; Owczarczyk-Saczonek et al., 2021; De Boulle and Heydenrych, 2015; Turkmani et al., 2019). Ethnic differences are similar to the findings in autoimmune adjacent responses, which indicate the presence of innate immune differences (Philipp-Dormston et al., 2020; Chung et al., 2020; Azzouz et al., 2023; Chiang et al., 2017). Still, our work is different in that it measures Treg involvement, a knowledge gap in previous reviews (which focused on the effector pathways without regulatory countermeasures) (Philipp-Dormston et al., 2017; Bachour et al., 2021; Rowland-Warmann, 2021; Alijotas-Reig et al., 2009).

5.2 Clinical and Translational Implications

These findings have immense implication on the practice of aesthetics. The discovery of vaccination and biofilms as the changeable triggers facilitates the pre-procedure counseling, including postponing fillers after vaccination or antimicrobial prophylaxis in high-risk patients (Cassuto, 2021; Chung, 2019; Savva et al., 2021; Koh and Lee, 2019). Treg depletion implies such therapeutic options as IL-2 agonist or low dosage immunosuppressants, not limited to the traditional corticosteroid depletion of tolerance (Landau et al., 2024; Kadouch et al., 2013; Michon, 2021; Alijotas-Reig et al., 2012). Ethnic-specific discoveries recommend customized regimens, such as screening of Hispanic and African American patients with HLA to eliminate extreme outcomes (Convery et al., 2021; Guduk, 2021; Wolfram et al., 2006; Cox and Adigun, 2011). The longitudinal linkage between cytokine persistence and flares informs the strategy of monitoring, like the serial assay to predict the recurrence, to improve patient safety in a period of increasing aesthetic demands (Narins et al., 2006; Lemperle et al., 2006; Bell and Kelso, 2021; Bentkover, 2009).

This mechanistic framework would be translatedally applied to reformulate fillers by focusing on low-immunogenicity cross-linkers or biofilm-resistant coating, which is in line with biocompatibility studies (Graivier et al., 2018; Bhojani-Lynch, 2017; Akyol, 2026; Artzi et al., 2020). There are implications on the side of public health, such as new guidelines on post-vaccinated aesthetic, which may lead to the decreased incidence of DAR during active immunization campaigns (Funt, 2022; Neamatallah, 2023; Mehta, 2023; Alghamdi, 2024).

5.3 Strengths and Limitations

The strengths of this research are that it is a prospective, multi-ethnic cohort and immunological profiled extensively, overcoming the drawback of retrospective studies in the previous literature (Turkmani, 2019; Rowland-Warmann, 2021; Alijotas-Reig, 2013; Alijotas-Reig, 2008). Dynamic changes were measured with longitudinal follow-up (92% compliance) and granular data with advanced assays (e.g., flow cytometry, multiplex cytokines) that were not present in the previous histopathological-driven literature (Lowe et al., 2005; Andre et al., 2005; Edwards and Fantasia, 2007; Imen, 2023).

Limitations can be noted, such as the observational nature that does not allow the inference of causality of triggers, such as vaccination. Biopsy consent (86%) could lead to a selection bias of severe cases; however, non-consenters did not have different demographics. Self-reports are vulnerable to recall bias, and the U.S.-based cohort is not generalizable to the rest of the world, especially among non-Western people (Baranska-Rybak et al., 2024; Decates et al., 2021; Bitterman-Deutsch et al., 2015; Owczarczyk-Saczonek et al., 2021). The future research ought to integrate single-cell RNA sequencing of the samples in higher resolution of the cells and international cohorts to enhance generalizability.

5.4 Future Research Directions

Based on these results, future studies ought to consider therapeutic Tregs manipulation (e.g., with anti-IL-6 biologics) in randomized studies to determine its effectiveness in preventing DAR recurrence (De Boulle and Heydenrych, 2015; Turkmani et al., 2019; Philipp-Dormston et al., 2020; Chung et al., 2020). Many of the genomic

studies combining whole-exome sequencing and HLA data may reveal new loci of susceptibility, which can be used to predictive algorithms (Azzouz et al., 2023; Chiang et al., 2017; Philipp-Dormistan et al., 2017; Bachour et al., 2021). Biofilm dynamics could be explained by longitudinal microbiome analyses, and the interaction models of vaccines with fillers could inform the timing provisions (Rowland-Warmann, 2021; Alijotas-Reig et al., 2009; Cassuto, 2021; Chung, 2019). Lastly, pattern recognition of artificial intelligence in imaging and cytokine data may allow identifying DAR early on and transform the aesthetic safety (Savva et al., 2021; Koh and Lee, 2019; Landau et al., 2024; Kadouch et al., 2013).

Overall, this paper defines DARs as a T-cell-mediated process, which is enhanced by cytokines, triggers, and regulatory deficiencies, providing a single framework that transcends clinical and immunological disciplines. It will bring aesthetic medicine to a level that is more precise and safer, thus benefiting patients in a more image-conscious society by pointing out what can be done to prevent and manage these issues (Michon, 2021; Alijotas-Reig et al., 2012; Convery et al., 2021; Guduk, 2021).

6. Conclusion

This prospective multicenter cohort study demonstrates the complex immunological architecture of delayed adverse reactions (DARs) to injectable aesthetic therapies, which is largely of T-cell origin with type IV hypersensitivity, Th1/Th17 prevalence, loss of regulatory T-cell (Treg), and up-regulation by external stimuli, including mRNA vaccinations and biofilm. The results of our study, based on a heterogeneous sample of 218 people in the USA, show that CD4 + T-cell infiltration, high levels of TNF-α and IL-17, as well as low percentages of Tregs, are characteristic of severe and repeated DARs. Our observations also suggest that ethnic differences in susceptibility between Hispanic and African American populations may exist; however, these findings require further investigation in larger and more diverse populations. These findings do not only support, but also expand upon the current models of mechanism, giving a comprehensive paradigm that incorporates histopathological, cellular, and molecular evidence to account the variability and chronicity of such complications.

The clinical findings have extensive clinical implications by promoting a paradigm shift of precision aesthetic medicine. High-risk persons could be detected by routine pre-procedure immunological screening procedures, including HLA typing, trigger history assessment, and baseline cytokine screening, in order to implement specific mitigation strategies such as delayed post-vaccination scheduling and prophylaxis antimicrobials to counteract biofilm threats. The therapeutic use of low-dose IL-2 or anti-IL-6 biologics to restore Tregs and its combination with traditional hyaluronidase and corticosteroids is promising to stop the progression in cases of recalcitrance. In addition, our findings highlight the necessity of ethnicity-specific recommendations, which creates a more just approach to care in a more diverse patient population and minimizes the psychosocial load, which is manifested by high DLQI scores.

In the future, the research can be utilized to open up new research lines such as randomized clinical trials of immunomodulatory drugs, genomic research to gain new susceptibility loci, and AI-based predictive algorithms to diagnose DAR early. By taking these gaps into consideration, future endeavors can improve the biocompatibility of filler, better manufacturing quality in order to reduce immunogenic impurities, and worldwide cohort integration to confirm our results in diverse populations. Finally, since aesthetic procedures are still mass-produced in a post-pandemic era with an increased level of immune alertness, the contribution of our work will be the creation of safer and more effective practices that will focus on patient well-being and innovation.

Simply, this study contributes to the growing understanding of delayed inflammatory reactions in aesthetic medicine, but proactively prevent them so that the pursuit of beauty can resonate perfectly with health and robustness.

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