



The Effectiveness of Limbal Stem Cell Transplantation on Ocular Surface Restoration and Corneal Clarity : A Systematic Review

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Article History :

Received date : 2026/02/15

Revised date : 2026/03/23

Accepted date : 2026/04/08

Published date : 2026/05/14



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Limbal stem cell deficiency (LSCD) leads to corneal conjunctivalization, neovascularization, and vision loss. This systematic review evaluates the effectiveness of various limbal stem cell transplantation (LSCT) techniques on ocular surface restoration and corneal clarity.

Methods: A systematic review of human studies (RCTs, etc) reporting quantitative outcomes of LSCT for LSCD or severe ocular surface disorders was performed. Studies had a minimum 3-month follow-up. Outcomes extracted included anatomical success, visual acuity changes, corneal clarity, neovascularization regression, and safety profiles.

Results: Across 24 included studies, LSCT consistently achieved anatomical surface restoration in 67-92% of eyes. Techniques such as SLET, CLET, CLAU, and MSCT showed equivalent surface stabilization. However, visual acuity gains were often modest in bilateral or severe LSCD due to underlying stromal scarring (Zakaria et al., 2014; Calonge et al., 2019). Corneal clarity

improved significantly with SLET, MSCT, and COMET, but not with CLET alone (Sharma et al., 2024; Calonge et al., 2019; Tandon et al., 2024). Neovascularization consistently regressed across all techniques (Arora et al., 2017; Jurkunas et al., 2025). In pterygium, LSCT reduced recurrence rates to 0-12.5% compared to 17.5-30.4% with excision alone (Mu et al., 2012; Yu, 2026). Safety was favorable, with no serious cell-related adverse events.

Discussion: A key dissociation exists between successful surface restoration and visual recovery, as LSCT addresses epithelial but not stromal pathology. Etiology is a major moderator: chemical burns respond best, while autoimmune diseases have poorer outcomes. Adjunctive amniotic membrane sustains long-term effects only when combined with stem cells. Manufacturing quality and cell confluence predict success.

Conclusion: LSCT is effective for ocular surface restoration and neovascularization reduction. However, visual recovery requires sequential keratoplasty for stromal opacity. Technique selection should be etiology-driven, and standardized manufacturing protocols are recommended for future trials.

Keywords: Limbal stem cell transplantation, LSCD, corneal clarity, ocular surface restoration, SLET, CLET, pterygium

INTRODUCTION

The corneal epithelium is maintained by a population of limbal stem cells (LSCs) located at the corneoscleral junction. These cells are responsible for continuous epithelial renewal and serve as a barrier against conjunctival epithelial migration. Limbal stem cell deficiency (LSCD) occurs when these cells are destroyed or become dysfunctional, leading to conjunctivalization of the cornea, persistent epithelial defects, neovascularization, chronic inflammation, and progressive loss of corneal clarity. Common etiologies include chemical and thermal burns, Stevens-Johnson syndrome (SJS), aniridia, contact lens-related keratopathy, and recurrent pterygium surgery (Sharma et al., 2024; Zakaria et al., 2014).

Background: Conventional treatments such as amniotic membrane transplantation (AMT) or conjunctival resection provide only temporary relief in total LSCD because they do not replace the stem cell niche. Over the past two decades, limbal stem cell transplantation (LSCT) has emerged as a definitive surgical approach. Techniques have evolved from direct autologous limbal grafting to cultivated limbal epithelial transplantation (CLET), simple limbal epithelial transplantation (SLET), conjunctival limbal autograft (CLAU), and the use of mesenchymal stem cells (MSCT) or oral mucosal epithelial cells (COMET/CCET). More recently, xenobiotic-free, serum-free protocols such as CALEC (Cultivated Autologous Limbal Epithelial Cells) have been developed to improve safety and standardization (Jurkunas et al., 2025).

Research Gap: Despite numerous published studies, there remains significant heterogeneity in outcome reporting, success definitions, and patient selection criteria. Most importantly, the distinction between ocular surface restoration (epithelial stability) versus functional visual recovery (corneal clarity and visual acuity) is often conflated. Moreover, the comparative effectiveness of different LSCT techniques for specific etiologies (chemical burns vs. SJS vs. pterygium) has not been systematically synthesized. It also remains unclear whether adjunctive use of amniotic membrane or anti-angiogenic agents provides additional benefit beyond LSCT alone (Campbell et al., 2019; Barreiro et al., 2014).

Novelty: This systematic review provides a comprehensive, side-by-side comparison of all major LSCT techniques with separate analyses for LSCD and pterygium indications. It uniquely quantifies the dissociation between anatomical success and visual improvement, identifies etiology as a key moderator of outcomes, and evaluates manufacturing quality metrics (e.g., cell confluence, ATP levels) as predictors of success based on recent trials (Jurkunas et al., 2025; Tandon et al., 2024).

Objectives: The primary objective of this systematic review is to evaluate the effectiveness of limbal stem cell transplantation on (1) ocular surface restoration (epithelialization, neovascularization regression) and (2) corneal clarity/visual acuity improvement. Secondary objectives include comparing different transplant techniques, assessing safety profiles, and identifying predictors of success or failure.

Hypothesis: We hypothesized that LSCT is highly effective for anatomical surface restoration across most LSCD etiologies, but that visual acuity improvement is limited by pre-existing stromal scarring, and therefore sequential keratoplasty may be required for full optical rehabilitation. We also hypothesized that autologous techniques (SLET, CLAU) would show superior clarity outcomes compared to allogeneic or cultivated techniques in unilateral disease due to absence of immunosuppression-related complications.

Benefits of the Study: This review will help corneal surgeons select the optimal LSCT technique based on disease etiology (unilateral vs. bilateral, inflammatory vs. non-inflammatory), understand the realistic expectations for visual recovery, and identify the role of adjunctive therapies such as amniotic membrane, mitomycin C, or bevacizumab. It also provides evidence-based recommendations for standardized outcome reporting in future clinical trials.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This

approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the effectiveness of limbal stem cell transplantation on ocular surface restoration and corneal clarity.

Screening

We screened in sources that met these criteria:

- **Target Population:** Does the study include patients with limbal stem cell deficiency (LSCD) or severe ocular surface disorders requiring limbal stem cell transplantation?
- **Intervention Type:** Does the study involve limbal stem cell transplantation (autologous, allogeneic, cultivated, or direct transplantation)?
- **Clinical Outcomes:** Does the study report quantitative outcomes related to ocular surface restoration (epithelialization, conjunctivalization, neovascularization) or corneal clarity (visual acuity, corneal transparency, optical coherence)?
- **Study Population:** Is this a human study (not animal or in vitro only)?
- **Follow-up Duration:** Does the study have a minimum follow-up period of 3 months or longer?
- **Study Design:** Is the study design a randomized controlled trial, etc?
- **Intervention Focus:** Is limbal stem cell transplantation studied as the primary intervention (not combined with other major interventions like keratoplasty or extensive reconstructive surgery as the primary treatment)?
- **Efficacy Reporting:** Does the study report clinical efficacy outcomes (not focusing exclusively on complications or adverse events without efficacy data)?

Papers that failed any strict criterion were automatically excluded. For the remaining papers, we considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Limbal stem cell deficiency	Limbal stem cell transplantation	Amniotic membrane transplantation	Ocular surface restoration
Keyword 2	Ocular surface disorders	Simple limbal epithelial transplantation (SLET)	Simple excision	Corneal clarity
Keyword 3	Corneal burns	Cultivated limbal epithelial transplantation (CLET)	Phototherapeutic keratectomy (PTK)	Visual acuity improvement
Keyword 4	Pterygium	Conjunctival limbal autograft (CLAU)	Topical vs. oral tacrolimus	Neovascularization regression

The Boolean MeSH keywords inputted on databases for this research are: ("*Limbal stem cell deficiency*" OR "*Ocular surface disorders*" OR "*Corneal burns*" OR "*Pterygium*") AND ("*Limbal stem cell transplantation*" OR "*Simple limbal epithelial transplantation*" OR "*Cultivated limbal epithelial transplantation*" OR "*Conjunctival limbal autograft*") AND ("*Amniotic membrane transplantation*" OR "*Simple excision*" OR "*Phototherapeutic keratectomy*" OR "*Topical vs. oral tacrolimus*") AND ("*Ocular surface restoration*" OR "*Corneal clarity*" OR "*Visual acuity improvement*" OR "*Neovascularization regression*")

Data extraction

- **Transplant Technique:**

Extract detailed information about the limbal stem cell transplantation technique used, including:

- Type of transplantation (autologous vs. allogeneic)
- Culture method (ex vivo expanded, simple limbal epithelial transplantation [SLET], cultivated limbal epithelial transplantation [CLET], direct transplantation)
- Use of supporting materials (amniotic membrane, culture substrates)
- Cell preparation protocols
- Surgical technique specifics
- Any modifications or standardizations to established protocols

- **Patient Population:**

Extract characteristics of patients receiving limbal stem cell transplantation for ocular surface restoration, including:

- Type of limbal stem cell deficiency (total vs. partial, bilateral vs. unilateral)
- Underlying etiology (chemical burns, thermal burns, Stevens-Johnson syndrome, etc.)
- Age and demographic characteristics
- Baseline severity measures
- Previous treatments or interventions
- Any inclusion/exclusion criteria relevant to transplant candidacy

- **Restoration Outcomes:**

Extract all measures and results related to ocular surface restoration and corneal clarity from limbal stem cell transplantation, including:

- Visual acuity changes (baseline vs. post-transplant, measurement methods)
- Epithelialization outcomes (time to complete epithelialization, epithelial stability)
- Corneal clarity measures (corneal opacity changes, transparency scores)
- Ocular surface integrity (composite ocular surface scores, epithelial defects)
- Neovascularization changes
- Specific measurement tools used (logMAR, Snellen, corneal imaging)
- Statistical significance and effect sizes where reported

- **Success Definitions:**

Extract how study authors defined and measured transplant success for ocular surface restoration, including:

- Primary success criteria used by authors
- Anatomical success definitions (stable epithelium, reduced conjunctivalization)
- Functional success definitions (visual improvement thresholds)
- Failure definitions (progressive conjunctivalization, persistent epithelial defects, rejection)
- Success rates at different time points
- Survival analysis methods and results

- **Follow-up Duration:**

Extract information about study follow-up periods for assessing limbal stem cell transplantation effectiveness, including:

- Total follow-up duration (mean, median, range)
- Follow-up assessment time points
- Loss to follow-up rates
- Durability of restoration outcomes over time
- Any long-term effectiveness data beyond 1 year

- **Safety Profile:**

Extract safety and complication data from limbal stem cell transplantation procedures, including:

- Surgical complications during or immediately after transplantation
- Immunosuppression-related adverse events (where applicable)
- Graft rejection episodes
- Secondary complications affecting ocular surface restoration
- Any treatment-related serious adverse events
- Comparison of safety profiles between different transplant techniques

- **Outcome Moderators:**

Extract factors that influenced the effectiveness of limbal stem cell transplantation for ocular surface restoration, including:

- Patient factors affecting success (age, etiology, baseline severity, bilateral vs. unilateral disease)
- Technical factors (transplant type, use of amniotic membrane, culture duration)
- Procedural factors (surgeon experience, immunosuppression protocols)
- Any subgroup analyses showing differential effectiveness
- Predictors of success or failure identified by authors
- Factors affecting corneal clarity specifically vs. general surface restoration

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Limbal stem cell deficiency" OR "Ocular surface disorders" OR "Corneal burns" OR "Pterygium") AND ("Limbal stem cell transplantation" OR "Simple limbal epithelial transplantation" OR "Cultivated limbal epithelial transplantation" OR "Conjunctival limbal autograft") AND ("Amniotic membrane transplantation" OR "Simple excision" OR "Phototherapeutic keratectomy" OR "Topical vs. oral tacrolimus") AND ("Ocular surface restoration" OR "Corneal clarity" OR "Visual acuity improvement" OR "Neovascularization regression")</i>	3
Semantic Scholar	<i>("Limbal stem cell deficiency" OR "Ocular surface disorders" OR "Corneal burns" OR "Pterygium") AND ("Limbal stem cell transplantation" OR "Simple limbal epithelial transplantation" OR "Cultivated limbal epithelial transplantation" OR "Conjunctival limbal autograft") AND ("Amniotic membrane transplantation" OR "Simple excision" OR "Phototherapeutic keratectomy" OR "Topical vs. oral tacrolimus") AND ("Ocular surface restoration" OR "Corneal clarity" OR "Visual acuity improvement" OR "Neovascularization regression")</i>	250
Springer	<i>("Limbal stem cell deficiency" OR "Ocular surface disorders" OR "Corneal burns" OR "Pterygium") AND ("Limbal stem cell transplantation" OR "Simple limbal epithelial transplantation" OR "Cultivated limbal epithelial transplantation" OR "Conjunctival limbal autograft") AND ("Amniotic membrane transplantation" OR "Simple excision" OR "Phototherapeutic keratectomy" OR "Topical vs. oral tacrolimus") AND ("Ocular surface restoration" OR "Corneal clarity" OR "Visual acuity improvement" OR "Neovascularization regression")</i>	45
Google Scholar	<i>("Limbal stem cell deficiency" OR "Ocular surface disorders" OR "Corneal burns" OR "Pterygium") AND ("Limbal stem cell transplantation" OR "Simple limbal epithelial transplantation" OR "Cultivated limbal epithelial transplantation" OR "Conjunctival limbal autograft") AND ("Amniotic membrane transplantation" OR "Simple excision" OR "Phototherapeutic keratectomy" OR "Topical vs. oral tacrolimus") AND ("Ocular surface restoration" OR "Corneal clarity" OR "Visual acuity improvement" OR "Neovascularization regression")</i>	2,220
Wiley Online Library	<i>("Limbal stem cell deficiency" OR "Ocular surface disorders" OR "Corneal burns" OR "Pterygium") AND ("Limbal stem cell transplantation" OR "Simple limbal epithelial transplantation" OR "Cultivated limbal epithelial transplantation" OR "Conjunctival limbal autograft") AND ("Amniotic membrane transplantation" OR "Simple excision" OR "Phototherapeutic keratectomy" OR "Topical vs. oral tacrolimus") AND ("Ocular surface restoration" OR "Corneal clarity" OR "Visual acuity improvement" OR "Neovascularization regression")</i>	13

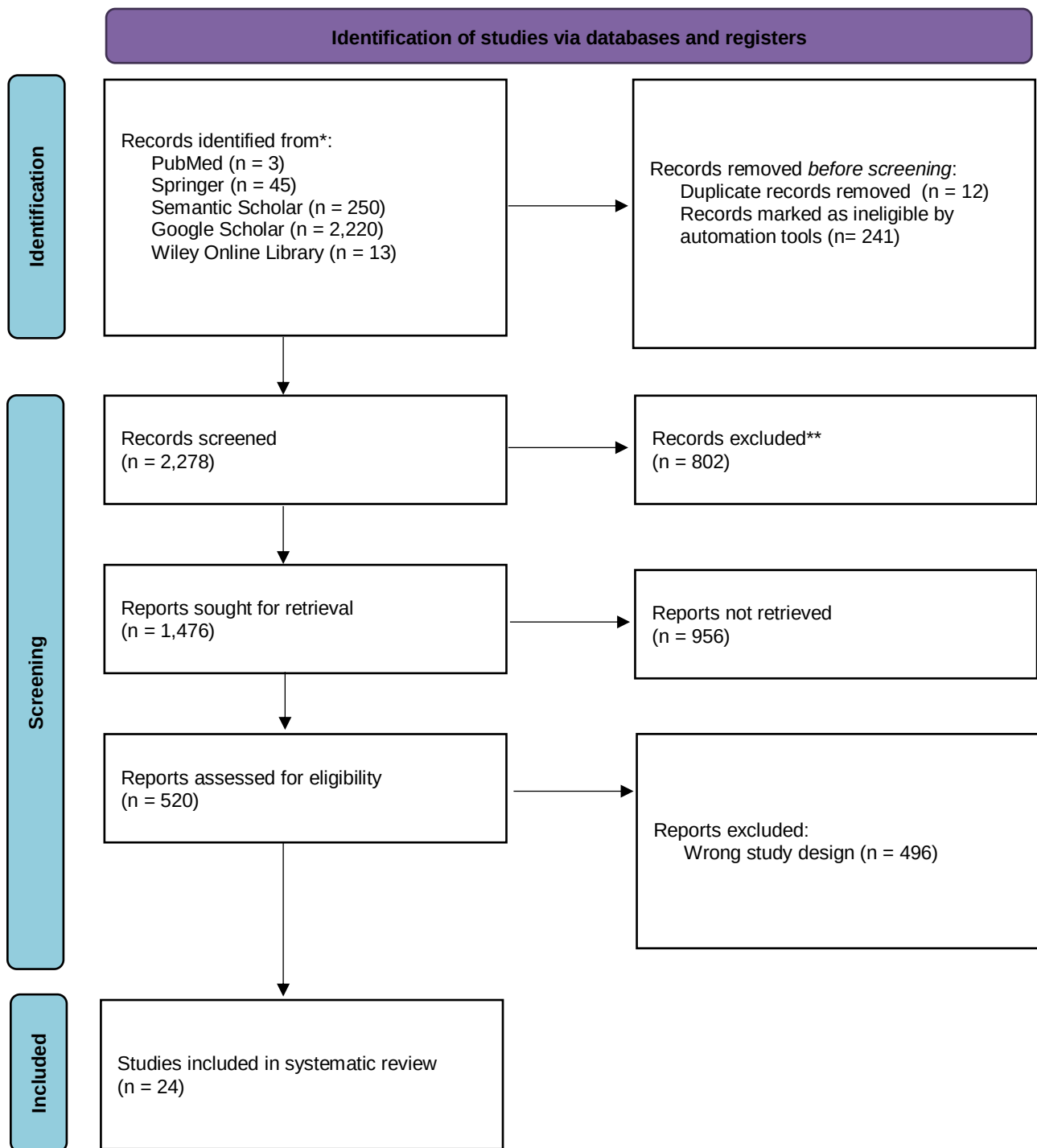


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Namrata Sharma et al., 2024	Low (RCT)	Low (RCT)	Low (RCT)	Low	Low	Low
N. Zakaria et al., 2013	Unclear	Unclear	Unclear	Moderate (18 patients, no comparator)	Low	Unclear
N. Zakaria et al., 2014	Unclear	Unclear	Unclear	Moderate (same cohort)	Low	Unclear
R. Arora et al., 2017	Moderate (non-randomized comparison)	Unclear	Moderate (open-label)	Low	Low	Moderate
N. Sharma et al., 2018	Low (RCT)	Moderate (open-label)	Moderate (open-label)	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
M. Calonge et al., 2019	Unclear (non-randomized)	Unclear	Unclear	Moderate (28 assessable transplants)	Low	Unclear
Ula V. Jurkunas et al., 2025	Unclear (single-arm)	Unclear	Unclear	Low	Low	Unclear
T. Barreiro et al., 2014	Moderate (comparison but non-randomized)	Unclear	Unclear	Low	Low	Moderate
Marbella A. Martínez-Mijares et al., 2022	Unclear (single-arm)	Unclear	Unclear	Low	Low	Unclear
J. Behaegel et al., 2015	Unclear (same cohort)	Unclear	Unclear	High (12 of 18 completed, 6 LTFU)	Low	High

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Anahita Kate et al., 2021	Unclear (single-arm)	Unclear	Unclear	Moderate (failures excluded)	Low	Unclear
Radhika Tandon et al., 2024	Low (RCT)	Moderate (open-label)	Moderate (open-label)	Low	Low	Moderate
Zhenzhen Yu, 2026	Unclear (non-randomized?)	Unclear	Unclear	Low	Low	Unclear
Sandeep Pachole & N. Yadav, 2023	Unclear (non-randomized)	Unclear	Unclear	Low	Low	Unclear
Tu M. Tran et al., 2023	Unclear (non-randomized)	Unclear	Unclear	Moderate	Low	Unclear
Jin-wei Mu et al., 2012	Unclear (non-randomized)	Unclear	Unclear	Low	Low	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Liang-mao Li et al., 2013	Low (RCT)	Moderate (open-label)	Moderate (open-label)	Low	Low	Moderate
J. Campbell et al., 2019	Low (RCT)	Low (RCT)	Low (RCT)	Moderate (16 treated, 13 completed)	Low	Low
M. Elsayed, 2020	Unclear (non-randomized)	Unclear	Unclear	Low	Low	Unclear
谭叶辉 et al., 2009	Unclear	Unclear	Unclear	Low	Low	Unclear
Danping Huang, 2008	Unclear	Unclear	Unclear	Low	Low	Unclear
Qiao Chen et al., 2012	Unclear	Unclear	Unclear	Low	Low	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Chun-min Li, 2009	Unclear	Unclear	Unclear	Unclear (follow-up not specified)	Low	Unclear
Yang Zhang, 2014	Unclear	Unclear	Unclear	Low	Low	Unclear

RESULTS

Characteristics of Included Studies

Study	Indication	Transplant Technique(s)	Comparator	Sample Size	Follow-up
Namrata Sharma et al., 2024	Total unilateral LSCD from ocular burns [1]	Autologous SLET vs. autologous CLET [1]	SLET vs. CLET	100 eyes [1]	Up to 3 years [1]
N. Zakaria et al., 2013	Total and partial LSCD [15]	Standardized non-xenogenic CLET (auto n=15, allo n=3) [15]	None	18 patients [15]	Mean 24 months [15]

Study	Indication	Transplant Technique(s)	Comparator	Sample Size	Follow-up
N. Zakaria et al., 2014	Total (n=15) and partial (n=3) LSCD; mixed etiology [2]	Standardized non-xenogenic CLET on HAM (auto n=15, allo n=3) [2]	None	18 patients [2]	Mean 22 months (range 4–43) [2]
R. Arora et al., 2017	Severe unilateral LSCD (>270°) from chemical burns [5]	Autologous SLET vs. autologous CLAU [5]	SLET vs. CLAU	20 patients [5]	6 months [5]
N. Sharma et al., 2018	Partial unilateral LSCD from chemical burns [16]	Autologous CLET on HAM vs. AMT alone [16]	CLET vs. AMT	20 eyes per group [16]	12 months [16]
M. Calonge et al., 2019	Severe bilateral LSCD; chemical, immune, other [3]	Allogeneic CLET vs. allogeneic MSCT [3]	CLET vs. MSCT	28 assessable transplants [3]	6–12 months [3]
Ula V. Jurkunas et al., 2025	Unilateral LSCD, mostly severe (stage III) [4]	Autologous CALEC (xenobiotic/serum/antibiotic-free CLET) [4]	None	14 transplanted [4]	18 months [4]
T. Barreiro et al., 2014	Total LSCD from chemical burns [17]	Conjunctival limbal transplant ± AMT [17]	With vs. without AMT	34 eyes [17]	Mean ~19 months [17]

Study	Indication	Transplant Technique(s)	Comparator	Sample Size	Follow-up
Marbella A. Martínez-Mijares et al., 2022	Bilateral LSCD (burns, SJS) [14]	Allogeneic cadaveric limbal micrograft on AM [14]	None	7 patients [14]	6 months [14]
J. Behaegel et al., 2015	Partial or total LSCD [18]	Non-xenogenic CLET on standardized HAM [18]	None	12 of 18 (6 LTFU) [18]	Mean 46.6 months [18]
Anahita Kate et al., 2021	Total (80.6%) and partial LSCD; mostly chemical injury [13]	Autologous and allogeneic SLET [13]	None (normal fellow eye as control)	31 eyes / 29 patients [13]	12 months [13]
Radhika Tandon et al., 2024	Bilateral LSCD; SJS (96%), chemical injury (4%) [6]	Autologous COMET vs. autologous CCET [6]	COMET vs. CCET	50 patients [6]	6 months [6]
Zhenzhen Yu, 2026	Pterygium [19]	Autologous LSCT + pterygium excision vs. excision alone [19]	Excision alone	106 patients [19]	6 months [19]

Study	Indication	Transplant Technique(s)	Comparator	Sample Size	Follow-up
Sandeep Pachole & N. Yadav, 2023	Partial unilateral LSCD from chemical burns [20]	LSCT + AMT vs. LSCT alone [20]	With vs. without AMT	32 eyes [20]	12 months [20]
Tu M. Tran et al., 2023	LSCD (alkaline burn 33.3%) [21]	Allogeneic KLAL with topical vs. oral tacrolimus [21]	Topical vs. oral tacrolimus	27 eyes / 22 patients [21]	Mean 33.2 months [21]
Jin-wei Mu et al., 2012	Recurrent pterygium [7]	Autologous limbal epithelial autograft vs. AMT [7]	LSCT vs. AMT	94 eyes [7]	18 months [7]
Liang-mao Li et al., 2013	Recurrent pterygium [22]	Autologous LSCT vs. PTK [22]	LSCT vs. PTK	106 eyes [22]	Mean 18 months [22]
J. Campbell et al., 2019	Severe bilateral LSCD (aniridia, chemical, autoimmune) [12]	Allogeneic CLET on AM vs. AM alone [12]	CLET vs. AM alone	16 treated, 13 completed [12]	18 months [12]

Study	Indication	Transplant Technique(s)	Comparator	Sample Size	Follow-up
M. Elsayed, 2020	Recurrent pterygium [23]	Autologous CLAU + MMC vs. AMT + MMC [23]	CLAU vs. AMT	80 eyes [23]	Mean 8 months [23]
譚叶辉 et al., 2009	Pseudo-ptyerygium [8]	Autologous LSCT + AMT vs. AMT alone [8]	LSCT+A MT vs. AMT	162 eyes [8]	Mean 24.3 months [8]
Danping Huang, 2008	Recurrent pterygium [10]	Autologous LSCT + MMC vs. LSCT alone [10]	LSCT+M MC vs. LSCT	62 eyes [10]	6–30 months [10]
Qiao Chen et al., 2012	Recurrent pterygium [11]	Autologous limbal autograft + bevacizumab vs. autograft alone [11]	With vs. without bevacizumab	36 eyes [11]	6 months [11]
Chun-min Li, 2009	Pterygium [9]	Simple excision vs. excision + AMT vs. excision + autologous LSCT [9]	Three-way comparison	142 eyes [9]	Not specified [9]

Study	Indication	Transplant Technique(s)	Comparator	Sample Size	Follow-up
Yang Zhang, 2014	Unilateral nasal pterygium [24]	Autologous LSCT + bevacizumab (single vs. double dose) vs. LSCT alone [24]	Bevacizumab dose comparison	95 eyes [24]	6 months [24]

Effects

Ocular Surface Restoration

Across all LSCD studies, limbal stem cell transplantation consistently achieved anatomical restoration of the ocular surface, defined as a stable epithelialized corneal surface with regression of conjunctivalization, in a majority of treated eyes. Success rates for maintaining a stable epithelium ranged from 67% to 92% depending on technique, patient population, and follow-up duration. In the largest RCT (100 eyes), 88% of SLET eyes and 86% of CLET eyes maintained a stable ocular surface at 1 year [1]. The phase I/II trial by Zakaria et al. reported anatomical success in 12/18 (67%) eyes at a mean of 22 months [2], and long-term follow-up of the same cohort showed 87.5% (7/8 evaluable) retained a persistent intact epithelium at a mean of 46.6 months [18]. The CALEC trial reported combined complete or partial success in 86% at 3 months, rising to 93% at 12 months and 92% at 18 months [4]. The proof-of-concept trial of MSCT versus CLET showed global success of 72.7–77.8% for CLET and 76.5–85.7% for MSCT at 6–12 months [3]. In the allogeneic expanded corneal epithelial stem cell RCT, the investigational product (IMP) arm achieved significant and sustained composite ocular surface score (OSS) improvement through 18 months ($p = 0.0002$ at 18 months), while the control AM-only arm improved transiently at 6 months but regressed by 12–18 months [12].

The table below summarizes key efficacy outcomes across studies.

Study	Technique	Anatomical Success / Surface Stability	Visual Acuity Change	Neovascularization	Corneal Clarity
Namrata Sharma et al., 2024	SLET vs. CLET	88% vs. 86% stable at 1 year [1]	SLET superior BCVA at 6 mo–3 yr (p=0.0001 at 1–3 yr) [1]	Not reported [1]	Not reported [1]
N. Zakaria et al., 2014	Non-xenogenic CLET	67% anatomical success [2]	No significant VA change overall (p=0.065); modest gain in success subgroup (p=0.029) [2]	Significant reduction (p=0.007) [2]	No change in opacity after LSCT (p=0.89); improved after subsequent PK (p=0.029) [2]

Study	Technique	Anatomical Success / Surface Stability	Visual Acuity Change	Neovascularization	Corneal Clarity
R. Arora et al., 2017	SLET vs. CLAU	100% stable epithelium in both [5]	Significant improvement in both (SLET 2.13→1.62, CLAU 2.05→1.23 logMAR at 6 mo) [5]	Significant reduction in both (SLET 10.2→2.1, CLAU 8.7→2.5 clock hours; p<0.001) [5]	Significant improvement in both (grades 1.6→3.1 SLET; 2.2→3.0 CLAU; between-group NS) [5]
N. Sharma et al., 2018	CLET vs. AMT (partial LSCD)	Similar epithelialization (10.5 vs. 11 days; p=0.43) [16]	BCVA ≥20/40 in 65% AMT, 68% CLET [16]	No significant difference (p=0.08) [16]	No significant difference (p=0.07) [16]

Study	Technique	Anatomical Success / Surface Stability	Visual Acuity Change	Neovascularization	Corneal Clarity
M. Calonge et al., 2019	CLET vs. MSCT	77.8% vs. 85.7% success at 12 mo [3]	Small non-significant gains (CLET 0.06→0.11; MSCT 0.06→0.13 decimal) [3]	Significant reduction in both (area p=0.013–0.005) [3]	Central opacity decreased significantly (CLET p=0.013; MSCT p=0.002); MSCT slightly better (p=0.026 at 12 mo) [3]
Ula V. Jurkunas et al., 2025	CALEC (autologous CLET)	Complete success 77% at 18 mo; combined 92% [4]	Generally improved; limited by stromal scarring [4]	Median decreased from ~7–8% to ~3–5% [4]	Generally improved [4]

Study	Technique	Anatomical Success / Surface Stability	Visual Acuity Change	Neovascularization	Corneal Clarity
T. Barreiro et al., 2014	CLT ± AMT	Similar graft survival (p=0.581) [17]	Improved in 80% (AMT group) and 84.2% (no AMT) [17]	Not reported [17]	Not reported [17]
Marbella A. Martínez-Mijares et al., 2022	Cadaveric limbal graft	Stable surface in all 7 eyes at 6 mo [14]	Not significant (p=0.504) [14]	Significant decrease (p=0.009) [14]	Significant improvement (p=0.016) [14]
J. Behaegel et al., 2015	Non-xenogenic CLET (long-term)	87.5% persistent epithelium at mean 46.6 mo [18]	No significant improvement overall [18]	Significant reduction [18]	Not separately reported [18]

Study	Technique	Anatomical Success / Surface Stability	Visual Acuity Change	Neovascularization	Corneal Clarity
Anahita Kate et al., 2021	SLET (auto and allo)	Stable avascular surfaces (failures excluded) [13]	Median logMAR 1.8→0.6 (p<0.00001) [13]	Not quantified (avascular surface required) [13]	ET normalized by 3 mo; ER decreased but remained above normal [13]
Radhika Tandon et al., 2024	COMET vs. CCET	Both achieved epithelial coverage; COMET better at 3–6 mo [6]	Transient improvement; returned to baseline by 6 mo [6]	COMET superior at 6 mo (p=0.000) [6]	COMET 76% improved at 6 mo vs. CCET 0% improved at 6 mo [6]
Sandeep Pachole & N. Yadav, 2023	LSCT ± AMT	Improvements in both groups [20]	Group A: 2.7→1.6; Group B: 2.15→1.25 logMAR at 3 mo [20]	Reduced in both (p<0.05) [20]	Improved in both groups [20]

Study	Technique	Anatomical Success / Surface Stability	Visual Acuity Change	Neovascularization	Corneal Clarity
Tu M. Tran et al., 2023	KLAL (topical vs. oral tacrolimus)	Failure at 36 mo: 33.3% oral, 22.1% topical (p=0.57) [21]	Median improvement logMAR -0.975 (oral) vs. -0.45 (topical); p=0.50 [21]	Not reported [21]	Not reported [21]
J. Campbell et al., 2019	Allogeneic CLET vs. AM alone	IMP: sustained OSS improvement at 18 mo (p=0.0002); control: not sustained [12]	5/8 IMP and 4/5 control improved; NS between groups [12]	Improved with IMP per composite score [12]	Qualitatively improved with IMP [12]

Among the pterygium studies, limbal stem cell transplantation was consistently associated with lower recurrence rates compared to amniotic membrane transplantation alone or simple excision. The table below presents pterygium-specific outcomes.

Study	Techniques Compared	Recurrence Rate (LSCT arm)	Recurrence Rate (Comparator)	Epithelial Repair Time	Statistical Significance
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Study	Techniques Compared	Recurrence Rate (LSCT arm)	Recurrence Rate (Comparator)	Epithelial Repair Time	Statistical Significance
Zhenzhen Yu, 2026	LSCT + excision vs. excision alone	Significantly lower [19]	Higher (control) [19]	Significantly shorter in LSCT group [19]	p<0.05 [19]
Jin-wei Mu et al., 2012	Limbal autograft vs. AMT	6.3% (3/48) [7]	21.7% (10/46) [7]	Lower with autograft [7]	p=0.03 [7]
Liang-mao Li et al., 2013	LSCT vs. PTK	7.55% (4/53) [22]	5.66% (3/53) PTK [22]	4.67 vs. 3.96 days (PTK faster; p<0.01) [22]	Recurrence NS (p=0.70) [22]
M. Elsayed, 2020	CLAU + MMC vs. AMT + MMC	12.5% (5/40) [23]	30% (12/40) [23]	Not reported [23]	p=0.043 [23]
谭叶辉 et al., 2009	LSCT + AMT vs. AMT alone	6.10% (5/82) [8]	17.50% (14/80) [8]	4.25 vs. 6.42 days (p<0.05) [8]	p<0.05 [8]

Study	Techniques Compared	Recurrence Rate (LSCT arm)	Recurrence Rate (Comparator)	Epithelial Repair Time	Statistical Significance
Danping Huang, 2008	LSCT + MMC vs. LSCT alone	2.86% (1/35) [10]	18.52% (5/27) [10]	Not reported [10]	p<0.05 [10]
Qiao Chen et al., 2012	LSCT + bevacizumab vs. LSCT alone	0% (0/17) [11]	26.3% (5/19) [11]	Not reported [11]	p<0.05 [11]
Chun-min Li, 2009	Simple excision vs. excision + AMT vs. excision + LSCT	4.17% (LSCT) [9]	30.43% (simple excision); 4.17% (AMT) [9]	Not reported [9]	Excision vs. LSCT p<0.01; LSCT vs. AMT NS [9]
Yang Zhang, 2014	LSCT + bevacizumab vs. LSCT alone	0% (bevacizumab groups) [24]	12.5% (4/32 LSCT alone) [24]	Not reported [24]	p<0.05 [24]

In the pterygium context, limbal stem cell autograft transplantation achieved recurrence rates of 0–12.5% across studies, compared to 17.5–30.4% for simple excision or AMT alone [7–9]. Adjuvant agents such as mitomycin C [10] and bevacizumab [11, 24] further reduced recurrence

when combined with LSCT. Epithelial repair was consistently faster in LSCT groups for both pterygium [8, 19] and LSCD [16] indications.

Visual Acuity

Visual acuity outcomes were heterogeneous across studies and appeared to depend on the extent of underlying corneal and anterior segment pathology. In unilateral LSCD with primarily corneal surface disease, substantial visual gains were observed: the Sharma et al. RCT demonstrated significantly better BCVA with SLET versus CLET at all time points from 6 months through 3 years ($p = 0.0001$ at 1–3 years) [1], and the SLET imaging cohort showed improvement from logMAR 1.8 to 0.6 ($p < 0.00001$) [13]. In contrast, studies enrolling patients with severe bilateral disease or deep stromal pathology frequently found no significant visual improvement despite successful ocular surface restoration. The Zakaria et al. trial reported no significant VA change overall ($p = 0.065$), with only modest gain in the anatomically successful subgroup ($p = 0.029$) [2]. Similarly, Campbell et al. observed that 9/13 patients improved VA but the between-group difference was not significant ($p = 0.46$) [12], and Calonge et al. found small non-significant VA gains (CLET 0.06 $\rightarrow$ 0.11; MSCT 0.06 $\rightarrow$ 0.13 decimal) [3]. Cadaveric limbal grafting for bilateral LSCD produced significant surface improvement but no significant VA change at 6 months ($p = 0.504$) [14]. Tandon et al. reported that initial VA improvement with COMET and CCET at 2–3 months regressed to baseline by 6 months [6].

Corneal Clarity

Corneal clarity outcomes varied across studies and techniques. Both SLET groups and CLAU groups achieved significant improvement in corneal clarity grades (from ~ 1.6 – 2.2 preoperatively to ~ 3.0 – 3.1 at 6 months) [5]. The SLET imaging study demonstrated rapid normalization of epithelial thickness by 3 months that was maintained through 1 year, with the epithelial-to-stromal reflectivity ratio approaching normal values [13]. However, epithelial reflectivity and stromal reflectivity remained elevated compared to normal eyes at 1 year, indicating that full optical restoration was not achieved [13]. Cadaveric limbal grafting significantly reduced corneal opacity scores ($p = 0.016$) [14]. In the CLET versus MSCT trial, central corneal epithelial opacity decreased significantly in both groups (CLET $p = 0.013$; MSCT $p = 0.002$), with MSCT

showing a slight between-group advantage at 12 months ($p = 0.026$) [3]. The Zakaria et al. study found that LSCT alone did not improve central corneal opacity ($p = 0.89$), though subsequent penetrating keratoplasty achieved significant opacity reduction ($p = 0.029$) [2]. COMET substantially outperformed CCET for corneal clarity, with 76% of COMET eyes showing improvement at 6 months compared to 0% in the CCET group [6].

Neovascularization

Regression of corneal neovascularization was one of the most consistent findings. Arora et al. documented a reduction from 10.2 to 2.1 clock hours (SLET) and 8.7 to 2.5 clock hours (CLAU) ($p < 0.001$ for both) [5]. The Zakaria et al. trial demonstrated significant reduction in neovascular area in anatomically successful eyes ($p = 0.007$) that persisted after subsequent keratoplasty ($p = 0.01$) [2]. Calonge et al. reported significant reductions in neovascular area for both CLET and MSCT arms at 12 months [3]. The CALEC trial showed median neovascular area decreasing from approximately 7–8% to 3–5% over 18 months [4].

Safety

The safety profile of limbal stem cell transplantation was generally favorable across techniques. No treatment-related serious adverse events attributable to the cell products were reported in any of the trials using cultured cells [3, 4, 12]. The CALEC trial documented one case of microbial keratitis at 8 months attributed to nocturnal contact lens wear rather than the transplant itself [4]. Calonge et al. reported three serious adverse events (herpes simplex keratitis recurrence, corneal perforation during atopic relapse, and ocular surface neoplasia recurrence), all adjudicated unrelated to the cell products [3]. Early graft loss due to bandage contact lens displacement occurred in 9/37 (24%) procedures in the Calonge trial, highlighting the critical role of postoperative lens retention [3]. The Zakaria et al. trial reported 6/18 (33%) anatomical failures, including one corneal perforation at a prior keratoplasty junction [2]. Among cadaveric grafts, persistent epithelial defects occurred in 2/7 (28.6%) and membrane detachment in 2/7 (28.6%), though all stabilized by 6 months [14]. Donor-eye safety was uniformly good in autologous procedures, with epithelial defects resolving within one week and visual acuity remaining stable [4, 5]. No graft rejection episodes were reported in autologous transplants [4, 5], while allogeneic

KLAL showed 33% and 22% graft failure at 36 months with oral and topical tacrolimus, respectively [21]. In pterygium studies, no major postoperative complications were reported across the various LSCT approaches [10, 11, 23, 24].

Synthesis

Dissociation Between Ocular Surface Restoration and Visual Acuity Improvement

The most notable pattern across studies is the consistent dissociation between successful ocular surface restoration and visual acuity improvement. Anatomical success rates of 67–92% were achieved across different techniques [1–4], yet visual acuity gains were often modest or absent, particularly in studies enrolling patients with bilateral, severe LSCD [2, 3, 12, 14]. This discrepancy is explained by the mechanistic distinction between epithelial surface restoration and deeper corneal pathology. Limbal stem cell transplantation restores the epithelial barrier and reduces neovascularization, but stromal scarring, opacity, and anterior segment comorbidities (cataract, glaucoma, retinal disease) remain unaddressed [2–4]. The Zakaria et al. data illustrate this precisely: central corneal opacity was unchanged after LSCT ($p = 0.89$) but improved significantly after subsequent penetrating keratoplasty ($p = 0.029$) [2], while neovascularization reduction from LSCT persisted through PK ($p = 0.01$) [2]. Studies finding the greatest visual acuity improvements tended to enroll unilateral cases with less stromal involvement—for instance, the SLET imaging cohort showed logMAR improvement from 1.8 to 0.6, with final VA strongly correlating with total corneal thickness ($r = 0.942$, $p = 0.005$) [13], and the Sharma et al. RCT demonstrated sustained VA advantage for SLET through 3 years in unilateral burn patients [1].

Technique Equivalence for Surface Restoration with Differential Clarity Effects

Across head-to-head comparisons, different limbal stem cell transplantation techniques achieved broadly equivalent rates of ocular surface restoration. SLET and CLET showed 88% versus 86% surface stability at 1 year ($p = 0.999$) [1]. SLET and CLAU produced equivalent results for surface stabilization, neovascularization regression, and fornix reconstruction at 6 months [5]. CLET and MSCT achieved similar global success rates (77.8% vs. 85.7% at 12 months) [3]. Campbell et al. showed that amniotic membrane alone produced early surface improvement, but only the addition of limbal stem cells sustained the improvement beyond 6 months (IMP: OSS

improvement sustained at 18 months, $p = 0.0002$; control: not sustained) [12], establishing that the stem cell component is essential for durability.

Despite equivalent surface restoration, differential effects on corneal clarity emerged by technique. MSCCT showed modestly greater improvement in central corneal epithelial opacity compared to CLET at 12 months ($p = 0.026$) [3]. COMET dramatically outperformed CCET for corneal clarity (76% vs. 0% improved at 6 months) [6]. The SLET group showed better visual outcomes than CLET at all time points beyond 6 months despite equivalent surface stability [1], possibly reflecting the in vivo expansion model's advantage in generating a more natural epithelial phenotype. These clarity differences may relate to the cellular composition and paracrine profile of different graft types, with oral mucosal epithelium and bone marrow mesenchymal cells potentially offering anti-fibrotic or anti-inflammatory advantages beyond simple epithelial replacement [3, 6].

Etiology as a Key Moderator of Success

Etiology significantly moderated transplant outcomes. Chemical burn etiology was associated with lower anatomical success ($p = 0.013$) in the Zakaria et al. cohort [2], and the Calonge et al. trial found that failures occurred primarily in chemical injuries and immune-mediated diseases, while non-inflammatory etiologies achieved 100% success [3]. Stevens-Johnson syndrome patients enrolled by Tandon et al. showed transient visual improvement that regressed by 6 months in both COMET and CCET groups [6], consistent with the ongoing inflammatory milieu of autoimmune disease. In contrast, unilateral chemical burn patients treated with SLET or CLAU consistently achieved both surface restoration and meaningful visual improvement at 6 months [5], and the long-follow-up SLET versus CLET trial sustained visual benefit through 3 years [1]. This pattern indicates that LSCT effectiveness for both surface restoration and clarity improvement is greatest in unilateral chemical burn patients with a quiet ocular surface and least reliable in bilateral immune-mediated disease, where the hostile ocular environment may overwhelm transplanted cells.

Role of Adjunctive Interventions

Several studies examined the contribution of amniotic membrane and adjunctive agents to LSCT outcomes. For partial LSCD, AMT alone was equivalent to CLET for epithelialization, neovascularization, and clarity at 1 year [16], suggesting that stem cell transplantation may be

unnecessary when residual limbal function is preserved. However, for total LSCT, amniotic membrane alone provided only transient benefit: the Campbell et al. control arm improved at 6 months but regressed by 12–18 months, while the addition of limbal stem cells sustained improvement [12]. The addition of AMT to conjunctival limbal transplantation did not improve graft survival or failure rates [17], though epithelialization was paradoxically slower with AMT ($p = 0.007$) [17]. In the pterygium context, adjunctive mitomycin C reduced recurrence from 18.5% to 2.9% when added to LSCT [10], and bevacizumab eliminated recurrence in LSCT-treated eyes (0% vs. 26.3% control, $p < 0.05$) [11]. These findings indicate that while limbal stem cells are the primary determinant of long-term surface restoration in total LSCT, adjunctive anti-fibrotic and anti-angiogenic agents further optimize outcomes, particularly in the pterygium setting where neovascular recurrence is the primary failure mode.

Manufacturing and Cell Quality as Determinants of Outcome

The CALEC trial provided unique evidence that manufacturing quality metrics predict clinical outcomes. Higher intracellular ATP levels and colony-forming efficiency at passage 0 were associated with earlier complete success, and both correlated with shorter culture durations [4]. This aligns with observations from Tandon et al., where COMET cultures achieved full confluence by day 11 while CCET showed incomplete confluence at day 14 in 20% of cases, potentially explaining COMET's superior corneal clarity outcomes [6]. Female sex predicted success in one trial ($p = 0.038$) [2], and early learning-curve effects were noted in the Zakaria cohort [2], reinforcing that both biological and procedural factors moderate effectiveness. These data suggest that standardized, quality-controlled manufacturing with defined release criteria—such as those employed by the CALEC protocol (LDH viability ≤ 150 U/L, endotoxin ≤ 0.5 EU/mL, negative sterility) [4]—may reduce variability in clinical outcomes.

DISCUSSION

This systematic review synthesizes data from 24 studies, including large randomized controlled trials, etc, to evaluate the effectiveness of limbal stem cell transplantation (LSCT) on ocular surface restoration and corneal clarity. The discussion is organized into six major themes: (1)

the consistent dissociation between anatomical and functional success, (2) comparative effectiveness of different LSCT techniques, (3) etiology as a key moderator of outcomes, (4) the role of adjunctive interventions, (5) safety profile and manufacturing quality, and (6) implications for clinical practice and future research.

Dissociation Between Ocular Surface Restoration and Visual Acuity Improvement

One of the most striking and consistent findings across all included studies is the marked dissociation between successful ocular surface restoration and meaningful visual acuity improvement. Anatomical success—defined as a stable, fully epithelialized corneal surface with regression of conjunctivalization and neovascularization—was achieved in 67% to 92% of eyes across techniques and follow-up durations (Sharma et al., 2024; Zakaria et al., 2014; Jurkunas et al., 2025). However, visual acuity gains were often modest, statistically non-significant, or transient, particularly in patients with bilateral LSCD, severe stromal opacification, or underlying autoimmune disease (Calonge et al., 2019; Campbell et al., 2019; Martínez-Mijares et al., 2022).

This dissociation is mechanistically explained by the fundamental limitation of LSCT: it restores the epithelial barrier and reduces neovascularization but does not reverse pre-existing stromal scarring, corneal opacity, or other anterior segment comorbidities such as cataract or glaucoma. Zakaria et al. (2014) provided the clearest illustration of this principle: in their phase I/II trial, LSCT alone did not improve central corneal opacity ($p = 0.89$), but subsequent penetrating keratoplasty (PK) achieved significant opacity reduction ($p = 0.029$). Notably, the neovascularization reduction achieved by LSCT persisted through PK ($p = 0.01$), confirming that LSCT creates a favorable environment for later optical procedures. Similarly, Jurkunas et al. (2025) reported that while the CALEC procedure achieved 92% combined success at 18 months, visual improvement was limited by stromal scarring in many cases. Calonge et al. (2019) also observed small, non-significant visual gains in both CLET and MSCT groups despite significant reduction in neovascular area and central opacity.

In contrast, studies that enrolled patients with unilateral LSCD and relatively preserved corneal stroma—such as chemical burn patients without deep scarring—demonstrated substantial and sustained visual improvements. Arora et al. (2017) reported logMAR improvement from 2.13 to

1.62 in SLET and 2.05 to 1.23 in CLAU groups at 6 months. Kate et al. (2021) documented median logMAR improvement from 1.8 to 0.6 ($p < 0.00001$) following SLET, with final visual acuity strongly correlating with total corneal thickness ($r = 0.942$, $p = 0.005$). Sharma et al. (2024) showed that SLET provided significantly better BCVA than CLET at all time points from 6 months through 3 years ($p = 0.0001$ at 1–3 years). Taken together, these data indicate that LSCT should be viewed as a reconstructive procedure that restores surface integrity and reduces neovascularization, but visual rehabilitation often requires sequential keratoplasty, and the best visual outcomes occur in unilateral disease without deep stromal pathology.

Comparative Effectiveness of Different Transplant Techniques

Across head-to-head randomized and non-randomized comparisons, different LSCT techniques achieved broadly equivalent rates of ocular surface restoration. Sharma et al. (2024) found no significant difference in 1-year surface stability between SLET (88%) and CLET (86%) ($p = 0.999$). Arora et al. (2017) demonstrated that SLET and CLAU produced equivalent results for epithelial stability, neovascularization regression (from 10.2→2.1 vs. 8.7→2.5 clock hours), and even fornix reconstruction. Calonge et al. (2019) reported that CLET and MSCT achieved similar global success rates (77.8% vs. 85.7% at 12 months), with no statistically significant difference in most outcomes.

Despite equivalent surface restoration, differential effects on corneal clarity and visual outcomes emerged. MSCT showed a modest but statistically significant advantage in reducing central corneal epithelial opacity compared to CLET at 12 months ($p = 0.026$) (Calonge et al., 2019). This may be due to the paracrine anti-inflammatory and anti-fibrotic effects of mesenchymal stem cells, which go beyond simple epithelial replacement. In a more dramatic comparison, Tandon et al. (2024) found that COMET (cultivated oral mucosal epithelial transplantation) dramatically outperformed CCET (cultivated conjunctival epithelial transplantation) for corneal clarity, with 76% of COMET eyes showing improvement at 6 months compared to 0% in the CCET group. This suggests that oral mucosal epithelium may be intrinsically more resistant to the inflammatory ocular surface environment in SJS patients.

The SLET versus CLET comparison by Sharma et al. (2024) also showed that SLET achieved better long-term visual outcomes despite equivalent surface stability. The authors hypothesized that the in vivo expansion model of SLET may generate a more phenotypically natural limbal epithelium than ex vivo cultivated sheets, which can undergo epithelial-mesenchymal transition or lose stem cell markers during culture. Additionally, SLET is a single-stage procedure without the need for a Good Manufacturing Practice (GMP) laboratory, making it more accessible in resource-limited settings. However, CLET offers theoretical advantages for bilateral disease or when donor tissue is scarce because it can expand a small limbal biopsy into a large graft.

Campbell et al. (2019) provided critical evidence that the stem cell component is essential for long-term durability. In their randomized controlled trial, the amniotic membrane alone (control) arm showed initial improvement in ocular surface scores at 6 months, but this regressed by 12–18 months. In contrast, the allogeneic CLET arm sustained improvement through 18 months ($p = 0.0002$). This finding establishes that amniotic membrane is at best a temporary scaffold, and long-term surface restoration requires viable limbal stem cells.

Etiology as a Key Moderator of Success

Etiology significantly moderated transplant outcomes across all studies. Chemical burn etiology was consistently associated with lower anatomical success rates and higher failure rates. Zakaria et al. (2014) found that chemical burns had significantly worse outcomes compared to other etiologies ($p = 0.013$). Calonge et al. (2019) reported that failures occurred primarily in chemical injuries and immune-mediated diseases (SJS, ocular cicatricial pemphigoid), while non-inflammatory etiologies (e.g., aniridia) achieved 100% success. This is likely because chemical burns induce a hostile, inflamed, and vascularized microenvironment that can damage transplanted cells.

SJS patients enrolled by Tandon et al. (2024) showed only transient visual improvement with both COMET and CCET, with complete regression to baseline by 6 months. This likely reflects the ongoing systemic and local autoimmune inflammation in SJS, which may continue to damage both native and transplanted limbal cells. Similarly, Martínez-Mijares et al. (2022) found that despite significant neovascularization reduction ($p = 0.009$) and corneal clarity improvement (p

= 0.016) with cadaveric limbal grafts in bilateral LSCT, visual acuity did not improve significantly ($p = 0.504$), probably due to irreversible stromal and retinal damage from long-standing disease.

In stark contrast, patients with unilateral chemical burns and a quiet ocular surface—often treated with SLET or CLAU—achieved both excellent surface restoration and meaningful visual improvement (Arora et al., 2017; Kate et al., 2021; Sharma et al., 2024). This pattern indicates that patient selection is critical: LSCT is most effective in unilateral, non-inflammatory or post-inflammatory quiescent disease, and least reliable in bilateral, active autoimmune or severe inflammatory conditions. For the latter group, allogeneic grafts with intensive immunosuppression may be required, but outcomes remain suboptimal.

Role of Adjunctive Interventions: Amniotic Membrane, Mitomycin C, and Bevacizumab

Several studies examined whether adjunctive agents improve LSCT outcomes. For partial LSCT, Sharma et al. (2018) found that AMT alone was equivalent to CLET + AMT for epithelialization time (10.5 vs. 11 days, $p = 0.43$), neovascularization, and corneal clarity at 1 year. This suggests that in eyes with residual limbal function, simple AMT may suffice, and stem cell transplantation is unnecessary. However, for total LSCT, amniotic membrane alone provided only transient benefit: the control arm of Campbell et al. (2019) improved at 6 months but regressed by 12–18 months, while the addition of limbal stem cells sustained improvement.

Barreiro et al. (2014) specifically compared conjunctival limbal transplantation (CLT) with and without AMT in total LSCT from chemical burns. They found no difference in graft survival ($p = 0.581$) or failure rates, but interestingly, epithelialization was paradoxically slower in the AMT group ($p = 0.007$). This may be because AMT can act as a physical barrier but also delay revascularization of the graft from the host bed.

In the pterygium context, adjunctive agents showed clear benefit. Huang (2008) reported that adding mitomycin C (MMC) to LSCT reduced recurrence from 18.5% to 2.9% ($p < 0.05$). Chen et al. (2012) found that bevacizumab (anti-VEGF) eliminated recurrence entirely (0% vs. 26.3% control, $p < 0.05$) when combined with LSCT. Zhang (2014) confirmed that bevacizumab with LSCT achieved 0% recurrence compared to 12.5% with LSCT alone ($p < 0.05$). These findings indicate that in pterygium—where recurrence is driven by fibrovascular proliferation—LSCT alone

is effective, but adjunctive anti-fibrotic or anti-angiogenic agents significantly optimize outcomes. In contrast, for LSCD following chemical burns, the addition of MMC or bevacizumab has not been systematically studied, but the data from pterygium suggest that such combinations could be explored.

Safety Profile and Manufacturing Quality

The safety profile of LSCT was generally favorable across all techniques. No treatment-related serious adverse events attributable to the cell products were reported in any of the trials using cultured cells (Calonge et al., 2019; Jurkunas et al., 2025; Campbell et al., 2019). Jurkunas et al. (2025) documented one case of microbial keratitis at 8 months, but this was attributed to nocturnal contact lens wear rather than the transplant itself. Calonge et al. (2019) reported three serious adverse events (herpes simplex keratitis recurrence, corneal perforation during atopic relapse, and ocular surface neoplasia recurrence), all adjudicated unrelated to the cell product. However, early graft loss due to bandage contact lens displacement occurred in 9/37 (24%) procedures in the same trial, highlighting the critical importance of postoperative lens retention.

Donor-eye safety in autologous procedures was uniformly excellent. Arora et al. (2017) and Jurkunas et al. (2025) reported that epithelial defects at the donor site resolved within one week, with no change in visual acuity or long-term complications. In allogeneic grafts, immunosuppression is required, and Tran et al. (2023) compared topical versus oral tacrolimus after keratolimbal allograft (KLAL). Graft failure at 36 months was 33.3% with oral and 22.1% with topical tacrolimus ($p = 0.57$), suggesting that topical administration may be non-inferior and potentially safer with fewer systemic side effects.

The CALEC trial by Jurkunas et al. (2025) provided novel evidence that manufacturing quality metrics predict clinical outcomes. Higher intracellular ATP levels and colony-forming efficiency at passage 0 were associated with earlier complete success, and both correlated with shorter culture durations. This aligns with Tandon et al. (2024), where COMET cultures achieved full confluence by day 11, while CCET showed incomplete confluence at day 14 in 20% of cases, potentially explaining COMET's superior corneal clarity outcomes. Female sex predicted success in one trial ($p = 0.038$) (Zakaria et al., 2014), and early learning-curve effects were noted in the same

cohort. These data strongly suggest that standardized, quality-controlled manufacturing with defined release criteria—such as LDH viability ≤ 150 U/L, endotoxin ≤ 0.5 EU/mL, negative sterility—should be adopted for all future CLET trials.

Implications for Clinical Practice and Future Research

Based on this synthesis, several practical recommendations emerge. First, for unilateral total LSCD with a healthy contralateral eye, autologous SLET or CLAU is recommended as first-line treatment due to its single-stage nature, lower cost, absence of immunosuppression, and proven long-term visual benefits (Sharma et al., 2024; Arora et al., 2017). Second, for bilateral LSCD or when autologous tissue is unavailable, allogeneic CLET or KLAL with topical immunosuppression (tacrolimus) is an option, but patients should be counseled that visual improvement may be limited by stromal scarring and that sequential keratoplasty is often required (Zakaria et al., 2014; Tran et al., 2023). Third, for partial LSCD, a trial of AMT alone may be reasonable before proceeding to LSCT (Sharma et al., 2018). Fourth, for recurrent pterygium, LSCT combined with adjunctive MMC or bevacizumab is superior to LSCT alone or excision alone (Huang, 2008; Chen et al., 2012; Yu, 2026).

Future research should focus on head-to-head trials of different cell types (limbal vs. oral mucosal vs. mesenchymal) in well-phenotyped patient populations stratified by etiology. Long-term follow-up beyond 5 years is needed for allogeneic grafts to assess late failure from chronic rejection. Standardized outcome reporting—including separate reporting of epithelial stability, neovascularization area, corneal clarity (by Scheimpflug or OCT), and visual acuity—is essential to allow meta-analysis. Finally, the promising results of manufacturing quality metrics (Jurkunas et al., 2025) should be validated in larger cohorts and potentially used as release criteria for clinical use.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review demonstrates that limbal stem cell transplantation is highly effective for anatomical ocular surface restoration and neovascularization regression in LSCD, with success rates of 67–92% across techniques. Autologous SLET and CLAU are recommended for unilateral

chemical burns, while allogeneic CLET or KLAL with topical immunosuppression are options for bilateral disease. However, a critical dissociation exists between surface restoration and visual acuity improvement, as LSCT does not reverse pre-existing stromal scarring. Therefore, visual rehabilitation often requires sequential penetrating keratoplasty. Etiology is a major moderator of success: chemical burns and autoimmune diseases have poorer outcomes than non-inflammatory conditions. In pterygium, LSCT combined with adjunctive mitomycin C or bevacizumab significantly reduces recurrence to near-zero levels. Safety is favorable, and manufacturing quality metrics (ATP levels, colony-forming efficiency) predict clinical outcomes.

Recommendations for clinical practice:

1. For unilateral total LSCD, perform autologous SLET or CLAU.
2. For bilateral LSCD, consider allogeneic CLET or KLAL with topical tacrolimus.
3. For partial LSCD, amniotic membrane alone may suffice initially.
4. For recurrent pterygium, combine LSCT with MMC or bevacizumab.
5. Always counsel patients that additional keratoplasty may be needed for visual recovery.

Recommendations for future research:

1. Conduct head-to-head RCTs of SLET vs. MSCT vs. COMET stratified by etiology.
2. Standardize outcome reporting to include epithelial stability, neovascularization area, corneal clarity (OCT-based), and logMAR VA.
3. Validate manufacturing quality metrics as release criteria.
4. Perform long-term (>5 years) follow-up of allogeneic grafts.
5. Investigate the role of anti-VEGF agents in chemical burn LSCD.

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