International Research Journal of Medical Sciences and Health Care (IRJMSHC)
eISSN: 3087-405X
Volume03 Issue07 | Page No: - 01-06

Received: 30 May 2026, Revised: 19 June 2026, Accepted: 25 June 2026, Published: 05 July 2026

DOI: https://doi.org/10.55640/irjmshc-v03i07-01

A Comprehensive Systematic Review and Evidence-Based Framework for Evaluating Limbal Stem Cell Transplantation in Ocular Surface Reconstruction and Corneal Transparency Restoration

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ABSTRACT: Limbal stem cell transplantation (LSCT) has emerged as a transformative therapeutic strategy for ocular surface reconstruction in patients with limbal stem cell deficiency (LSCD), a condition that leads to chronic epithelial instability, corneal opacity, and severe visual impairment. Despite significant advancements in surgical techniques such as simple limbal epithelial transplantation (SLET), cultivated limbal epithelial transplantation (CLET), keratolimbal allografts, and amniotic membrane-assisted procedures, clinical outcomes remain heterogeneous due to variations in patient selection, surgical protocols, and postoperative management strategies. This systematic review synthesizes current clinical evidence to evaluate the effectiveness of LSCT in restoring corneal clarity and ocular surface integrity while proposing an integrated evidence-based analytical framework for outcome assessment.

Findings from randomized controlled trials and clinical comparative studies indicate that autologous and allogeneic limbal stem cell approaches significantly improve epithelial regeneration and visual rehabilitation, though success rates are influenced by disease severity, underlying etiology, and adjunctive therapies (Sharma et al., 2024). Comparative evidence further demonstrates variability between SLET and CLET approaches in ocular burn populations, highlighting the need for standardized evaluation metrics (Arora et al., 2017). The review identifies key gaps in long-term outcome consistency, immunological management, and objective imaging-based assessment tools.

An evidence-based framework is proposed integrating clinical grading scales, optical coherence tomography (OCT) biomarkers, and functional visual outcomes to standardize LSCT evaluation. This framework aims to enhance reproducibility, optimize patient stratification, and guide future translational research in corneal regenerative medicine.

KEYWORDS: Limbal stem cell transplantation, ocular surface reconstruction, corneal clarity, LSCD, SLET, CLET, amniotic membrane transplantation, regenerative ophthalmology, systematic review, evidence-based framework.

1.1 Introduction

1.1 Background

The corneal epithelium is maintained by a specialized population of limbal stem cells located at the corneoscleral junction, which ensure continuous epithelial renewal and maintenance of corneal transparency. Damage to this limbal niche due to chemical injury, trauma, infection, or autoimmune conditions results in limbal stem cell deficiency (LSCD), characterized by conjunctivalization of the corneal surface, chronic inflammation, neovascularization, and progressive vision loss.

Limbal stem cell transplantation (LSCT) has evolved as a cornerstone intervention aimed at restoring epithelial homeostasis. Techniques such as simple limbal epithelial transplantation (SLET), cultivated limbal epithelial transplantation (CLET), and keratolimbal allografts have demonstrated promising clinical outcomes in restoring ocular surface integrity. However, variability in surgical success rates and postoperative complications necessitates a structured evaluation of evidence-based effectiveness.

1.2 Research Problem

Despite significant progress in regenerative ophthalmology, there remains a lack of standardized outcome frameworks for evaluating LSCT procedures. Existing studies present heterogeneous methodologies, inconsistent follow-up durations, and varying definitions of surgical success. Furthermore, comparative effectiveness between different transplantation techniques remains inconclusive due to differences in study design and patient populations.

For instance, comparative analyses of SLET versus conjunctival limbal autograft in ocular burns reveal differential outcomes in epithelial stability and visual recovery, emphasizing the need for standardized evaluation metrics (Arora et al., 2017). Similar inconsistencies are observed across studies involving amniotic membrane transplantation and cultivated epithelial cell approaches.

1.3 Objectives

This study aims to:

1. Systematically evaluate clinical outcomes of limbal stem cell transplantation techniques.

2. Analyze comparative effectiveness across major LSCT modalities.

3. Identify methodological gaps in current literature.

4. Develop an evidence-based analytical framework for standardized outcome assessment.

1.4 Scope and Significance

The review focuses on clinical and translational studies involving LSCT in LSCD, ocular burns, and recurrent pterygium. By synthesizing findings from randomized trials and observational studies, this work contributes to establishing a unified evaluative model that can be used in clinical decision-making and future research design.

2. Literature Review

2.1 Evolution of Limbal Stem Cell Transplantation Techniques

Early approaches to LSCD management involved conjunctival limbal autografts and keratolimbal allografts, which provided partial restoration of epithelial function but were associated with donor site morbidity and immune rejection risks. Later innovations introduced amniotic membrane transplantation (AMT) as a scaffold to enhance epithelial regeneration and reduce inflammation.

Clinical comparative studies demonstrate that conjunctival limbal transplantation without AMT yields variable outcomes in chemical injury-induced LSCD, indicating the importance of microenvironmental support in epithelial regeneration (Barreiro et al., 2014). Similarly, combined approaches using AMT with autologous stem cell transplantation show improved epithelial stability in partial LSCD cases (Sharma et al., 2018).

2.2 Advancements in Cultivated and Autologous Stem Cell Therapies

Cultivated limbal epithelial transplantation (CLET) represents a significant advancement in regenerative ophthalmology, allowing ex vivo expansion of stem cells to overcome donor tissue limitations. Phase I/II clinical trials demonstrate that standardized, non-xenogenic CLET protocols yield favorable epithelial regeneration outcomes with reduced immunogenic risk (Zakaria et al., 2013; Zakaria et al., 2014).

Further advancements include cultivated autologous limbal epithelial cell (CALEC) transplantation, which eliminates xenobiotic components and enhances biological safety in clinical applications (Jurkunas et al., 2025). These innovations indicate a shift toward fully autologous, serum-free regenerative approaches.

2.3 Comparative Effectiveness of LSCT Modalities

Multiple comparative studies have evaluated LSCT modalities in diverse clinical contexts. SLET and CLET have been compared in ocular burn patients, revealing similar anatomical success but differences in recovery timelines and epithelial stability (Sharma et al., 2024). In addition, SLET demonstrates significant improvements in corneal epithelial thickness and reflectivity as measured by OCT imaging (Kate et al., 2021).

In recurrent pterygium management, LSCT combined with adjunct therapies such as mitomycin C or bevacizumab has shown improved recurrence control (Huang, 2008; Chen et al., 2012). However, outcomes vary depending on surgical technique and postoperative immunomodulation.

2.4 Role of Adjunctive Therapies and Biomaterials

Amniotic membrane transplantation plays a crucial role in enhancing epithelial healing and reducing inflammation. Studies demonstrate that AMT combined with LSCT improves outcomes in partial LSCD cases compared to LSCT alone (Pachole & Yadav, 2023). Similarly, pharmacological adjuncts such as tacrolimus provide immunosuppressive benefits in keratolimbal allograft procedures (Tran et al., 2023).

2.5 Identified Research Gaps

Despite extensive clinical research, several gaps persist:

- Lack of standardized outcome assessment metrics.
- Inconsistent imaging-based evaluation tools.
- Limited long-term comparative data across LSCT techniques.

- Insufficient integration of functional and anatomical outcome measures.

Importantly, comparative studies such as those conducted by (Arora et al., 2017) highlight variability in surgical success rates, reinforcing the need for structured analytical frameworks.

3. METHODOLOGY

3.1 Study Design and Systematic Review Framework

This study adopts a structured systematic review design integrated with an evidence synthesis framework to evaluate the effectiveness of limbal stem cell transplantation (LSCT) in ocular surface reconstruction and corneal clarity restoration. The methodological approach is grounded in comparative clinical evidence analysis, focusing on randomized controlled trials, prospective cohort studies, and interventional case series involving LSCT techniques such as simple limbal epithelial transplantation (SLET), cultivated limbal epithelial transplantation (CLET), keratolimbal allografts, and amniotic membrane-assisted procedures.

The conceptual foundation of this methodology is based on regenerative medicine evaluation theory, which emphasizes biological restoration, functional recovery, and structural integrity as core outcome domains. In LSCT, these domains translate into epithelial stability, visual acuity restoration, and corneal transparency.

3.2 Data Stratification and Analytical Dimensions

The review framework categorizes extracted evidence into three analytical dimensions:

1. Biological Restoration Dimension – evaluates epithelial regeneration, limbal niche restoration, and cellular integration.

2. Functional Outcome Dimension – assesses visual acuity improvement, corneal surface stability, and refractive performance.

3. Structural Integrity Dimension – focuses on corneal clarity, vascularization reduction, and OCT-based morphological restoration.

These dimensions are aligned with clinical evidence from studies demonstrating that epithelial regeneration following LSCT is closely linked with long-term visual rehabilitation outcomes (Sharma et al., 2024).

3.3 Comparative Evaluation Model

A comparative analytical model is constructed to evaluate LSCT modalities. The model integrates:

- Surgical technique variables (SLET, CLET, keratolimbal allograft)

- Adjunct therapies (AMT, mitomycin C, bevacizumab, tacrolimus)

- Donor source classification (autologous, allogeneic, cadaveric)

- Clinical indication severity (partial vs total LSCD)

For example, comparative clinical data suggest that SLET and conjunctival limbal autograft yield different epithelial recovery trajectories in ocular burns, emphasizing procedure-dependent variability (Arora et al., 2017).

3.4 Evidence-Based Framework for Outcome Evaluation

An integrative framework is proposed for standardized LSCT assessment, consisting of four hierarchical layers:

Layer 1: Clinical Baseline Stratification

Patients are categorized based on LSCD severity, etiology (chemical burn, autoimmune, traumatic), and prior surgical history.

Layer 2: Surgical Intervention Mapping

Each LSCT technique is classified according to stem cell source, cultivation method, and scaffold utilization.

Layer 3: Outcome Measurement Indicators

Includes:

- Corneal epithelial stability

- Neovascularization regression

- Visual acuity improvement

- OCT-based epithelial thickness mapping (Kate et al., 2021)

Layer 4: Longitudinal Outcome Tracking

Involves follow-up periods extending beyond 12–24 months to assess graft survival and recurrence risk.

This multi-layered framework enhances reproducibility and minimizes heterogeneity in outcome reporting.

3.5 Analytical Rationale and Theoretical Basis

The methodology is grounded in regenerative epithelial biology, which posits that limbal stem cell niches regulate corneal homeostasis. Disruption of this niche leads to conjunctival epithelial invasion and loss of transparency. LSCT aims to re-establish this biological equilibrium through stem cell repopulation and microenvironmental restoration.

Evidence from cultivated stem cell trials supports this regenerative principle, particularly in xenobiotic-free CALEC transplantation models that demonstrate improved safety and biological compatibility (Jurkunas et al., 2025).

3.6 Limitations of Methodological Approach

Despite its structured design, the methodology is limited by heterogeneity in clinical trial protocols, variability in surgical expertise, and inconsistent reporting standards across studies. Additionally, differences in follow-up duration and outcome definitions reduce comparability across datasets.

4. RESULTS / FINDINGS

significantly improves ocular surface stability and corneal clarity across diverse etiologies of limbal stem cell deficiency (LSCD). Across included studies, epithelial restoration was achieved in a majority of cases undergoing autologous or allogeneic transplantation, though outcomes varied depending on surgical technique and disease severity.

Simple limbal epithelial transplantation (SLET) consistently demonstrated high anatomical success rates in unilateral LSCD, particularly in ocular burns. Comparative evidence indicates that SLET provides faster epithelial recovery compared to conjunctival limbal autografts, although long-term stability may depend on adjunctive therapy and postoperative management (Arora et al., 2017). Optical coherence tomography-based assessments further confirm improved epithelial thickness and reflectivity following SLET, indicating structural restoration of the corneal surface (Kate et al., 2021).

Cultivated limbal epithelial transplantation (CLET) shows comparable anatomical success with enhanced control over graft composition. Phase I/II trials of standardized non-xenogenic CLET protocols demonstrate stable epithelial regeneration with reduced immunological complications (Zakaria et al., 2013; Zakaria et al., 2014). Similarly, CALEC transplantation introduces a clinically significant advancement by eliminating serum and antibiotic exposure, improving biosafety and regenerative consistency (Jurkunas et al., 2025).

Adjunctive therapies significantly influence outcomes. Amniotic membrane transplantation (AMT) enhances epithelial adherence and reduces inflammation, particularly in partial LSCD cases. Studies show improved clinical outcomes when LSCT is combined with AMT compared to LSCT alone (Sharma et al., 2018; Pachole & Yadav, 2023). Pharmacological immunosuppression using tacrolimus in keratolimbal allografts further improves graft survival by reducing immune-mediated rejection (Tran et al., 2023).

In recurrent pterygium cases, LSCT combined with antimetabolites such as mitomycin C or anti-VEGF agents demonstrates reduced recurrence rates and improved corneal surface regularization (Huang, 2008; Chen et al., 2012). However, variability in recurrence outcomes suggests that adjunctive therapy alone cannot compensate for inadequate stem cell restoration.

Comparative clinical studies also highlight variability in outcomes between autologous and allogeneic grafts. Autologous procedures generally exhibit higher success rates due to reduced immune rejection risk, whereas allogeneic grafts require long-term immunosuppression and carry increased complication risks.

Overall, the findings indicate that LSCT is highly effective in restoring corneal epithelial integrity and improving visual outcomes, but success is strongly influenced by surgical technique, adjunctive therapy, and baseline disease severity. The heterogeneity of outcome measures across studies underscores the necessity for a standardized evaluation framework to ensure consistency in clinical reporting and research comparability.

5. DISCUSSION

The findings of this systematic review underscore the transformative potential of limbal stem cell transplantation in restoring ocular surface integrity and corneal transparency. However, the variability in outcomes across studies highlights fundamental challenges in standardizing regenerative ophthalmic interventions.

From a theoretical perspective, LSCT operates on the principle of limbal niche regeneration, wherein transplanted stem cells repopulate the damaged corneal epithelium and re-establish homeostatic epithelial turnover. This biological mechanism is consistently supported across autologous and allogeneic transplantation models, reinforcing the regenerative validity of LSCT as a therapeutic paradigm.

Clinically, the superiority of SLET and CLET over traditional conjunctival limbal autografts is evident in improved epithelial stability and reduced recurrence of conjunctivalization. However, comparative evidence also suggests that no single technique is universally superior, as outcomes depend heavily on patient-specific variables such as LSCD severity, ocular surface inflammation, and prior surgical interventions.

The integration of adjunctive therapies such as amniotic membrane transplantation and immunosuppressive agents introduces additional complexity. While AMT enhances epithelial healing by providing a biological scaffold, its efficacy is contingent on underlying stem cell viability. Similarly, pharmacological agents like tacrolimus improve graft survival but introduce systemic and ocular side-effect considerations (Tran et al., 2023).

A major limitation identified across studies is the lack of standardized outcome metrics. Most clinical trials rely on subjective grading systems for corneal clarity and epithelial stability, which limits reproducibility. Imaging-based modalities such as OCT provide more objective measures, yet are not uniformly adopted across clinical studies. This inconsistency significantly affects cross-study comparability.

Importantly, evidence from comparative clinical trials such as (Arora et al., 2017) highlights variability in surgical outcomes between SLET and conjunctival limbal autografts, reinforcing the need for structured evaluation frameworks. These inconsistencies suggest that current LSCT research is still in a transitional phase between experimental innovation and standardized clinical application.

The proposed evidence-based framework addresses this gap by integrating biological, functional, and structural outcome dimensions. By standardizing evaluation criteria, this model has the potential to enhance clinical decision-making and improve the reproducibility of research findings.

Despite these advances, several limitations persist. Long-term graft survival data remain limited, particularly for newer techniques such as CALEC transplantation. Additionally, immune-mediated complications in allogeneic transplantation continue to pose significant challenges. Variability in surgical expertise and institutional protocols further contributes to inconsistent outcomes.

Future research should focus on multicenter randomized controlled trials with standardized outcome reporting systems and extended follow-up periods. Integration of artificial intelligence-based imaging analysis may further enhance objective assessment of corneal restoration.

6. Conclusion

Limbal stem cell transplantation represents a cornerstone advancement in ocular surface reconstruction, offering substantial improvements in corneal clarity and visual rehabilitation. Evidence indicates that both autologous and allogeneic techniques are effective, though outcomes vary based on surgical method, adjunctive therapy, and disease severity. The study highlights the urgent need for standardized evaluation systems to harmonize clinical reporting and improve translational consistency.

The proposed evidence-based framework provides a structured approach to assessing LSCT outcomes across biological, functional, and structural domains. Future advancements in regenerative ophthalmology should prioritize long-term outcome validation, standardized imaging integration, and optimization of stem cell delivery systems.

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