Essentia:
Journal of Medical Practice and Research
Vol 2 No 2 December 2026, Hal 01-19
ISSN: 3123-4100(Print) ISSN: 3123-4097(Electronic
Open Access: https://scriptaintelektual.com/essentia

Which Pediatric Keratoconus Eyes Re-Progress After Corneal Cross-Linking? A Systematic Review of Long-Term Failure Rates and Clinical, Tomographic, and Protocol-Related Predictors

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Article Info :
Received:
10-10-2026
Revised:
02-11-2026
Accepted:
19-11-2026

Abstract

Corneal collagen cross-linking (CXL) effectively limits pediatric keratoconus progression, although long-term treatment failure remains a clinical concern. This systematic review evaluated postoperative failure rates and clinical, tomographic, and treatment-related predictors of re-progression in children and adolescents. Five databases were searched on 19 September 2026 following PRISMA 2020 guidelines. Eligible studies involved pediatric patients undergoing CXL with at least 12 months of follow-up. Two reviewers independently screened studies and assessed methodological quality using QUIPS, while evidence certainty was evaluated using GRADE. Narrative synthesis was performed because progression definitions differed across studies. Twenty-one studies involving 1,967 eyes from 1,387 patients across 11 countries were included. Failure rates ranged from 0% to 28.4% at 12–24 months and from 9.1% to 34% beyond seven years. Repeat CXL occurred in 1.7%–3.3% of eyes, while keratoplasty occurred in 1.7%–3.2%. Transepithelial CXL demonstrated consistently higher failure rates than epithelium-off procedures. Thinner corneas, decentered cones, and younger age were associated with increased progression, whereas baseline keratometry and ocular allergy showed inconsistent associations. Evidence certainty was predominantly low to very low. Long-term surveillance and standardized progression criteria remain necessary to improve postoperative risk assessment.

***Keywords**: Corneal cross-linking, Keratoconus, Paediatric, Prognostic factors, Treatment failure.*

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INTRODUCTION

Pediatric keratoconus represents a substantial challenge in contemporary ophthalmic practice because its onset during a period of ocular development is frequently accompanied by rapid corneal deformation, progressive visual impairment, and an extended lifetime risk of treatment-related complications. Population-based epidemiological evidence has challenged earlier assumptions regarding the rarity of keratoconus, reporting an annual incidence of approximately one case per 7,500 individuals and a prevalence of one per 375 individuals, although these estimates describe the broader population rather than children exclusively (Godefrooij et al., 2017). The clinical burden is particularly pronounced among pediatric patients because disease severity at presentation may be greater than that observed in adults, while progression can occur over comparatively shorter intervals. Evidence from a referral-based investigation demonstrated that 27.8% of eyes in patients aged 15 years or younger presented with advanced stage 4 keratoconus, compared with 7.8% of adult eyes, illustrating the potential consequences of delayed identification and intervention (Léoni-Mesplié et al., 2012). Corneal collagen cross-linking (CXL) has substantially altered the management of progressive keratoconus by providing a therapeutic approach intended to increase stromal biomechanical resistance and reduce further ectatic deterioration. The KERALINK randomized controlled trial established clinically meaningful evidence of treatment effectiveness among young patients, reporting progression in 2 of 30 cross-linked eyes compared with 12 of 28 eyes receiving standard care alone (Larkin et al., 2021). Nevertheless, successful initial stabilization does not establish permanent protection against subsequent corneal deterioration, particularly when patients remain under observation throughout adolescence and early adulthood. Long-term clinical monitoring has therefore become increasingly relevant as treatment objectives extend beyond immediate stabilization toward

the identification of delayed re-progression, the prevention of irreversible visual impairment, and the determination of appropriate surveillance strategies. The central clinical uncertainty concerns not simply whether CXL is effective in pediatric keratoconus, but which treated eyes remain vulnerable to subsequent progression and how that vulnerability can be identified using information available before treatment.

Existing evidence concerning pediatric CXL has developed through two related research directions: the comparative evaluation of treatment effectiveness and the identification of clinical characteristics associated with postoperative progression. Systematic evidence addressing overall treatment outcomes has demonstrated that corneal stabilization is achievable in most pediatric eyes, although the frequency of subsequent progression varies considerably across study populations, treatment protocols, and follow-up intervals. A pooled analysis encompassing 37 studies and 2,078 eyes estimated postoperative progression at 9.9%, with a 95% confidence interval of 6.1%–14.6%, while identifying substantial heterogeneity between the included investigations (Achiron et al., 2022). Comparative protocol studies suggest that epithelial status may be an important determinant of treatment durability, as a randomized investigation identified substantially greater progression following transepithelial CXL than following accelerated or conventional epithelium-off procedures (Iqbal et al., 2020). A separate prospective comparison extending to five years similarly identified postoperative progression in the transepithelial group but not in the conventional epithelium-off group, supporting the relevance of treatment protocol characteristics beyond short-term clinical outcomes (Henriquez et al., 2020). Research examining patient-specific prognostic characteristics has followed a complementary direction, associating reduced corneal thickness and paracentral cone location with greater progression risk after CXL (Sarac et al., 2016). Age-related differences have also been investigated, with one comparative pediatric cohort identifying substantially higher postoperative progression among children aged 14 years or younger than among older adolescents (Ozer et al., 2020). These studies collectively indicate that postoperative stabilization cannot be interpreted solely as a uniform treatment effect, because anatomical characteristics, developmental stage, and procedural differences may influence the durability of corneal stabilization. The contemporary evidence base consequently supports a multidimensional understanding of pediatric CXL outcomes, although the relative importance and consistency of individual prognostic factors remain incompletely established.

The principal research gap arises from the limited integration of long-term treatment failure estimates, baseline prognostic characteristics, and differences in the operational definitions used to determine postoperative progression. Existing pooled estimates provide useful information regarding average failure frequency but cannot independently establish whether between-study variation reflects differences in patient susceptibility, treatment protocols, observation periods, or outcome classification (Achiron et al., 2022). The distinction is particularly consequential because studies evaluating postoperative progression have applied different keratometric thresholds and tomographic parameters, potentially identifying different clinical events under the same terminology. Long-term evidence demonstrates the magnitude of this measurement problem, as an investigation involving 38 pediatric eyes followed for a mean of 11.6 years reported re-progression in 34% of eyes under a composite ABCD-based definition but only 7.9% when anterior curvature change was considered independently (Vinciguerra et al., 2023). Methodological assessments of keratoconus progression definitions have similarly emphasized that differences in measurement criteria influence clinical interpretation and decisions regarding disease progression (Koppen et al., 2024). Prognostic investigations present an additional limitation because baseline age, corneal thickness, cone position, and keratometric severity may be correlated, while relatively small failure populations restrict the capacity to distinguish independent associations. Although decreased pachymetry and paracentral cone location have been associated with postoperative progression, the corresponding estimates require interpretation in relation to the analytical designs and potential confounding of the underlying studies (Sarac et al., 2016). Age-related findings also require cautious interpretation because clinically meaningful differences between younger and older pediatric patients do not establish that age independently predicts failure after adjustment for disease severity and corneal morphology (Ozer et al., 2020). The unresolved scientific question therefore concerns which clinical, tomographic, behavioral, and treatment-related characteristics demonstrate reproducible associations with pediatric CXL failure when follow-up duration, outcome definition, and methodological limitations are

considered jointly. This gap cannot be resolved through a pooled failure proportion alone, because meaningful prognostic interpretation requires examination of the evidence underlying each reported association.

The scientific and clinical consequences of this uncertainty extend to postoperative surveillance, interpretation of tomographic changes, treatment selection, and the identification of children requiring prolonged ophthalmic follow-up. Pediatric patients who remain stable during early postoperative assessments may subsequently experience corneal deterioration, making surveillance decisions based exclusively on short-term outcomes potentially insufficient. Longitudinal evidence from a seven-year pediatric cohort indicates that progression can remain clinically relevant during later follow-up, supporting the need to distinguish initial treatment effectiveness from sustained stabilization (Polido et al., 2023). The consequences of delayed failure identification are particularly concerning because continued ectatic deterioration may necessitate additional treatment and complicate future visual rehabilitation. Conversely, uniformly intensive surveillance of all treated patients may impose considerable demands on clinical services without adequately distinguishing patients according to their probability of deterioration. Treatment selection introduces a related concern, as comparative evidence indicates that postoperative progression differs between epithelial preservation and epithelial removal protocols, although the magnitude of this difference must be interpreted alongside baseline characteristics and study design (Iqbal et al., 2020; Henriquez et al., 2020). The absence of consistent progression definitions further complicates clinical decision-making because a change interpreted as treatment failure under one tomographic criterion may not satisfy another, potentially influencing decisions regarding repeat intervention (Vinciguerra et al., 2023; Koppen et al., 2024). From a scientific standpoint, uncertainty regarding predictor consistency limits the translation of individual observational associations into reliable prognostic assessment and weakens comparisons between studies conducted across different clinical settings. A synthesis that distinguishes the timing of failure, the direction and strength of prognostic associations, and the certainty of the supporting evidence is therefore necessary to inform clinical interpretation without prematurely presenting incompletely validated predictors as definitive determinants of treatment failure.

The present systematic review is positioned at the intersection of long-term therapeutic outcome assessment and prognostic evidence synthesis, addressing a question that is not adequately answered by conventional evaluations of CXL effectiveness. Previous pooled research primarily quantified the frequency of postoperative progression, whereas comparative clinical studies concentrated on selected protocols or individual baseline characteristics (Achiron et al., 2022; Iqbal et al., 2020; Sarac et al., 2016). The proposed contribution is a structured integration of these evidence domains rather than the development of an unsupported new predictive model or the generation of additional primary clinical observations. The review specifically distinguishes failure estimates across predefined follow-up horizons, evaluates clinical and tomographic predictors alongside treatment-related characteristics, and examines how different definitions of progression influence the interpretation of reported outcomes. This approach addresses limitations arising from aggregating heterogeneous progression events and from comparing prognostic associations without considering their methodological foundations. Long-term cohorts provide the temporal basis for this assessment, demonstrating that postoperative outcomes may continue to change well beyond the initial stabilization period (Polido et al., 2023; Vinciguerra et al., 2023). Studies investigating age and baseline corneal morphology provide the clinical basis for evaluating whether proposed predictors are sufficiently consistent to support differentiated surveillance, rather than assuming that statistically significant associations from individual cohorts are universally applicable (Ozer et al., 2020; Sarac et al., 2016). Methodological scrutiny of progression definitions further provides a basis for separating potential biological re-progression from variation attributable to outcome classification (Koppen et al., 2024). The methodological contribution lies in the use of a prognostic-oriented narrative synthesis that retains distinctions among follow-up duration, treatment protocols, predictor domains, and outcome definitions while incorporating structured assessments of risk of bias and evidence certainty. The resulting synthesis is intended to clarify the strength and limitations of current knowledge, identify prognostic relationships supported by convergent evidence, and distinguish findings requiring further validation before application to individualized clinical management.

This systematic review aims to evaluate the frequency of keratoconus re-progression following corneal collagen cross-linking in children and adolescents and to identify baseline clinical, tomographic, behavioral, and treatment-protocol characteristics associated with subsequent treatment failure. The review specifically seeks to characterize reported progression rates according to follow-up duration, examine the frequency of repeat cross-linking and subsequent keratoplasty, assess the direction and consistency of associations between candidate prognostic factors and postoperative outcomes, and determine how differences in progression definitions influence the comparability of published findings. A further objective is to critically evaluate the methodological quality and certainty of the available evidence to distinguish relatively consistent prognostic indicators from associations affected by confounding, imprecision, or heterogeneous outcome assessment. The scientific contribution is expected to consist of a more differentiated synthesis of long-term pediatric CXL outcomes that moves beyond aggregate treatment effectiveness toward an evidence-informed interpretation of re-progression risk. The methodological contribution comprises an integrated assessment of outcome timing, prognostic domains, measurement heterogeneity, and evidence certainty without imposing quantitative synthesis on clinically incompatible endpoints. The practical contribution is to inform the selection of treatment protocols, the interpretation of postoperative corneal changes, and the development of more proportionate long-term surveillance strategies for pediatric patients at potentially increased risk of recurrent progression. These objectives establish a coherent analytical foundation for evaluating the durability of corneal stabilization and identifying priorities for subsequent prognostic research.

RESEARCH METHODS

This study employed a systematic review design to evaluate long-term treatment failure and prognostic factors associated with keratoconus re-progression following corneal collagen cross-linking (CXL) in pediatric patients. The review followed the PRISMA 2020 reporting framework, while narrative synthesis was structured according to the Synthesis Without Meta-analysis (SWiM) guideline. A review protocol was developed before study screening, although prospective registration remained pending. Five electronic databases, comprising PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane CENTRAL, were searched on 19 September 2026 without restrictions on publication date or language. The search strategy combined four conceptual domains using Boolean AND operators: keratoconus and related corneal ectatic disorders; CXL and related intervention terminology, including riboflavin; pediatric populations identified through free-text and controlled vocabulary terms; and postoperative outcomes encompassing progression, treatment failure, retreatment, keratoplasty, and prognostic factors. Eligible studies involved patients aged 18 years or younger undergoing CXL for progressive keratoconus, with at least 12 months of follow-up and extractable information concerning postoperative progression, retreatment, keratoplasty, intracorneal ring segment implantation, or baseline predictors. Randomized controlled trials, prospective and retrospective cohort studies, comparative studies, and case series involving at least 10 eyes were considered eligible. Studies involving adult populations without separately reported pediatric outcomes, non-keratoconus indications, insufficient follow-up, unavailable prognostic information, overlapping cohorts, or unclear progression outcomes were excluded, alongside case reports, reviews, conference abstracts, and protocols. One randomized contralateral-eye trial involving patients with Down syndrome aged 10–20 years was retained as a predefined exception to the pediatric age criterion, with its broader age range considered when evaluating indirectness. Two reviewers independently conducted title and abstract screening, full-text eligibility assessment, and methodological appraisal, resolving disagreements through discussion. The selection process involved 1,008 identified records, removal of 287 duplicates, screening of 721 records, and assessment of 133 available full-text reports after five reports could not be retrieved. Following exclusion of 112 full-text reports, 21 studies were retained for qualitative synthesis. Data were extracted using a structured workbook documenting study characteristics, geographical setting, design, participant and eye counts, age at treatment, CXL protocol, follow-up duration, progression definitions, treatment failure, retreatment, keratoplasty, and reported prognostic associations, including effect estimates and statistical significance where available. Bibliographic identifiers were independently verified through PubMed and Crossref, while unreported numerical information was neither estimated nor imputed.

The primary outcome was postoperative keratoconus re-progression or treatment failure according to the definition applied by each included study. Secondary outcomes comprised repeat CXL, keratoplasty, intracorneal ring segment implantation, changes in maximum or mean keratometry, ABCD progression parameters, corrected distance visual acuity deterioration, and reported adverse events, including corneal haze, sterile infiltrates, infection, and hydrops. Methodological quality was evaluated independently by both reviewers using the Quality in Prognosis Studies (QUIPS) instrument, which assesses six domains: study participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. Each domain was classified as presenting low, moderate, or high risk of bias, with written justifications supporting the overall assessment. Randomized allocation, where applicable, was considered within the participation and confounding assessments rather than evaluated using a separate instrument. Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering risk of bias, inconsistency, indirectness, and imprecision. Non-randomized prognostic evidence was initially classified as low certainty, while randomized evidence informed the certainty assessment of treatment-protocol comparisons. A narrative synthesis was performed because differences in progression thresholds, tomographic parameters, and follow-up intervals prevented clinically meaningful statistical pooling. Treatment failure, retreatment, and keratoplasty outcomes were organized into three follow-up categories: 12–24 months, 3–5 years, and at least 7 years. Prognostic characteristics were synthesized across nine domains covering treatment-related, clinical, tomographic, demographic, and behavioral factors, with each association evaluated according to its reported direction, quantitative strength, and consistency across studies. Differences in progression definitions were examined as a separate source of outcome heterogeneity rather than reconciled through an imposed common threshold. Subgroup analysis according to baseline keratoconus stage was not undertaken because only two studies reported stage-specific failure outcomes, while sensitivity analysis restricted to prospective studies was not considered informative because prospective and retrospective cohorts employed incompatible progression definitions. The synthesis retained study-specific outcome criteria and denominators, avoided unsupported numerical transformations, and incorporated methodological limitations into the interpretation of prognostic evidence to preserve analytical transparency and reproducibility.

RESULTS AND DISCUSSION

Study Selection and Characteristics of the Evidence on Pediatric Corneal Cross-Linking

The systematic identification of clinical evidence concerning pediatric corneal cross-linking revealed a heterogeneous research landscape characterized by differences in study design, treatment protocols, observation periods, and definitions of postoperative progression. The database search identified 1,008 records across five electronic sources, reflecting the substantial volume of literature addressing corneal ectasia and therapeutic stabilization in younger populations. The screening framework followed PRISMA 2020 principles to distinguish studies reporting clinically relevant postoperative outcomes from investigations focused primarily on procedural efficacy or short-term anatomical changes (Page et al., 2021). This distinction was necessary because an evaluation of treatment failure requires longitudinal evidence capable of identifying recurrent progression rather than merely demonstrating immediate postoperative keratometric improvement.

The initial screening process excluded 287 duplicate records, leaving 721 records for independent title and abstract assessment by two reviewers. Subsequent screening removed 583 records that did not meet the review objectives, while full-text retrieval was pursued for 138 reports, of which five were unavailable. The remaining 133 full-text reports underwent eligibility assessment, resulting in the exclusion of 112 reports and retention of 21 studies for narrative synthesis. The independent assessment procedure provided a structured basis for evidence selection, consistent with methodological expectations for systematic reviews involving prognostic factors and heterogeneous clinical outcomes (Page et al., 2021; Hayden et al., 2013).

The principal reasons for full-text exclusion reflected the methodological requirements of evaluating recurrent progression specifically among pediatric patients who had undergone corneal cross-linking. Adult or mixed-age populations without separately extractable pediatric outcomes accounted for 24 exclusions, while 21 reports lacked relevant long-term progression outcomes and 17 provided insufficient follow-up. Additional exclusions concerned the absence of extractable

prognostic characteristics, overlapping patient cohorts, non-keratoconus indications, and incomplete outcome definitions. These restrictions strengthened the alignment between the selected evidence and the review objectives, although the exclusion of studies with incomplete reporting also illustrates a recurrent limitation in prognostic research, where insufficiently specified outcomes constrain meaningful evidence synthesis (Hayden et al., 2013).

The selection process emphasized the distinction between studies capable of describing postoperative stabilization and those providing information about subsequent deterioration or treatment-related failure. Clinical studies evaluating pediatric cross-linking frequently employ keratometric stabilization as an indicator of effectiveness, but the duration of observation and the criteria used to establish progression differ considerably between investigations (Larkin et al., 2021; Iqbal et al., 2020). These differences influence whether the reported outcome represents early treatment response, recurrent disease progression, or a subsequent requirement for intervention. The identification and screening results are presented in Table 1, retaining the original search records, exclusion categories, and final study counts.

Table 1. PRISMA 2020 Flow of Study Identification, Screening and Selection

Stage	Details	n
Identification	PubMed 214; Embase 276; Scopus 248; Web of Science 187; CENTRAL 83	1,008
Before screening	Duplicates removed	287
Screening	Records screened / excluded	721 / 583
Full-text retrieval	Reports sought / unavailable	138 / 5
Eligibility	Full texts assessed / excluded	133 / 112
Exclusion reasons	Adult/mixed age 24; other indication 9; no outcome 21; short follow-up 17; no predictors 13; non-primary 11; overlap 8; unclear data 9	112
Included	Studies in narrative synthesis	21

Twenty-one studies published between 2016 and 2024 contributed 1,967 eyes from 1,387 patients in 11 countries. Eight originated in Turkey, while others represented Brazil, Egypt, India, Iran, Israel, Italy, the Netherlands, Peru, Saudi Arabia, and the United Kingdom. Cross-country differences in baseline severity and access to treatment may restrict transferability (Léoni-Mesplié et al., 2012; Padmanabhan et al., 2017).

The evidence comprised three randomized trials, seven prospective cohorts, and eleven retrospective investigations. Randomized studies examined protocol selection, CXL versus standard care, or contralateral-eye treatment in Down syndrome (Iqbal et al., 2020; Larkin et al., 2021; Hashemi et al., 2020). Observational designs supplied longer follow-up but were vulnerable to selection and indication confounding. Table 2 retains a compact listing of all 21 studies, including design, eye count, age, protocol, and failure criterion; R = retrospective, P = prospective, C = comparative, RCT = randomized controlled trial, and * denotes the predefined broader-age exception.

Table 2. Characteristics of The 21 Included Studies

Study	Setting / design	Eyes	Age (y)	CXL protocol	Follow-up; failure criterion
Sarac 2016	Turkey; R	72	14.8 ± 2.2	Standard epi-off	2 y; Kmax ≥1 D
Godefrooij 2016	Netherlands; P	54	Pediatric	Standard epi-off	≤5 y; ≥1 D
Padmanabhan 2017	India; P	377	8–18	Standard epi-off	≤6.7 y; loss of Kmax stability

Mazzotta 2018	Italy; P	62	≤18	Standard epi-off	10 y; Kmax >1 D / graft
Vinciguerra 2023	Italy; R	38	<18	Standard epi-off	Mean 11.6 y; ABCD
Ahmet 2024	Turkey; R	175	14.5 ± 2.2	Accelerated epi-off	10 y; tomography
Polido 2023	Brazil; P	74	13.0 ± 2.1	Standard epi-off	7 y; Kmax ≥1.5 D
Ağca 2020	Turkey; R	143	<18	Accelerated epi-off	4.2 y; K/Kmax ≥1 D
Ozer 2019	Turkey; R	35	13.0 ± 0.5	Accelerated epi-off	56 mo; tomography
Iqbal 2020	Egypt; RCT	271	Pediatric	Standard / accelerated / epi-on	2 y; keratometry
Sarac 2018	Turkey; R	87	<18	Standard / accelerated epi-off	2 y; keratometry
Simantov 2022	Israel; R	60	16.0 ± 2.1	Standard epi-off / fellow eye	7 y; need for treatment
Gupta 2022	India; P	116	14.8 ± 2.8	Epi-off in 50 eyes	2 y; persistent progression
Jamali 2023	Iran; R	7	13 at first CXL	Repeat epi-off	49.7 mo between CXLs
Larkin 2021	UK; RCT	58	10–16	Epi-off / standard care	18 mo; K2 ≥1.5 D
Henriquez 2020	Peru; P	78	≤18	Transepithelial / epi-off	5 y; keratometry
Hashemi 2020	Iran; RCT	54	10–20*	Accelerated / standard epi-off	2 y; zonal Kmax ≥1 D
Ozer 2020	Turkey; R	41	14.3 ± 1.8	Accelerated epi-off	2 y; keratometry
Alrobaian 2019	Saudi Arabia; R	89	<18	Standard epi-off	≥2 y; ectasia
Eraslan 2017	Turkey; C	36	12–18	Epi-off / epi-on	2 y; lack of stabilization
Uçakhan 2016	Turkey; P	40	15.2 ± 1.9	Standard epi-off	4 y; topography

Differences in cohort size constituted another important characteristic of the available evidence, particularly because postoperative treatment failure was not uniformly frequent across clinical populations. The largest investigation included 377 eyes, although only 194 eyes contributed follow-up observations extending beyond two years, creating potential concerns about attrition and the representativeness of long-term outcomes (Padmanabhan et al., 2017). At the opposite extreme, a retrospective investigation included seven eyes undergoing repeat cross-linking, providing clinically relevant descriptions of retreatment cases without an untreated or non-failing comparison group (Jamali et al., 2023). These differences indicate that larger cohorts may provide more informative estimates of failure frequency, while highly selected case series contribute contextual information about recurrent progression but cannot independently establish the predictive significance of baseline patient characteristics.

Treatment protocols also varied across the selected investigations, with eleven studies employing conventional epithelium-off cross-linking, six using accelerated epithelium-off procedures, and four comparing protocols that differed in epithelial status. These procedural variations are clinically relevant because conventional and accelerated irradiation protocols differ in treatment exposure, whereas transepithelial techniques preserve a barrier that may influence riboflavin penetration into the corneal stroma. Comparative investigations have examined these distinctions

through randomized and observational designs, creating opportunities to evaluate protocol-related differences in stabilization while retaining awareness of differences in baseline characteristics and treatment allocation (Eraslan et al., 2017; Henriquez et al., 2020; Iqbal et al., 2020). Treatment protocol heterogeneity consequently represents both a source of clinically meaningful comparative evidence and a potential explanation for variability between reported postoperative outcomes.

The duration of postoperative observation extended from 18 months to a mean of 11.6 years, allowing the evidence base to address early stabilization and longer-term corneal behavior. Studies with shorter observation periods provide information about treatment effectiveness during the initial postoperative phase, whereas extended longitudinal cohorts are better positioned to identify deterioration emerging several years after the original procedure. Long-term investigations extending to seven years or more demonstrate the availability of prolonged clinical observation, although differences in progression criteria complicate direct comparison between their reported outcomes (Mazzotta et al., 2018; Polido et al., 2023; Vinciguerra et al., 2023). Follow-up duration must consequently be treated as an essential analytical dimension rather than a secondary study characteristic, because the opportunity to observe late treatment failure depends directly on the length and completeness of postoperative surveillance.

Table 3. Risk of bias of the included studies assessed with QUIPS

Study	QUIPS D1–D6	Overall	Principal methodological consideration
Sarac 2016	L M L M M L	M	Unadjusted predictors; unmasked outcomes
Godefrooij 2016	L M L M M L	M	Small regression; eye-level unit of analysis
Padmanabhan 2017	L H L M H M	H	Long-term attrition; unadjusted subgroup findings
Mazzotta 2018	M H L L H M	H	Selected ten-year completer cohort
Vinciguerra 2023	M H L L H M	H	Selected completers; definition-sensitive failure
Ahmet 2024	L M L L M L	M	Retrospective; incomplete confounder adjustment
Polido 2023	L M L L M L	M	Nonrandom carrier comparison
Ağca 2020	L M L L H M	H	Unequal groups and treatment eras
Ozer 2019	M M L M H H	H	Small cohort; unadjusted effect estimates
Iqbal 2020	L L L L L M	L	Randomized protocols; allergy post hoc
Sarac 2018	L M L L M L	M	Protocol choice by era and preference
Simantov 2022	L M L M M M	M	One treated-eye repeat event
Gupta 2022	L L L M M M	M	Managed-cohort outcome denominator
Jamali 2023	H L M L H H	H	Retreatment-only sample of seven eyes
Larkin 2021	L L L L L L	L	RCT; prespecified progression endpoint
Henriquez 2020	L M L L M M	M	Nonrandomized protocol allocation
Hashemi 2020	L L L L L L	L	Contralateral randomized comparison
Ozer 2020	L L L M M M	M	Small unadjusted age subgroup
Alrobaian 2019	L L L M M L	M	Allergy comparison not adjusted for severity
Eraslan 2017	L L L L H M	M	Nonrandom epi-on/epi-off treatment
Uçakhan 2016	L L L M H M	M	Zero events; limited predictor evaluation

Table 3 retains concise QUIPS judgments for each study, and Figure 1 displays their six-domain distribution. D1–D6 represent participation, attrition, predictor measurement, outcome measurement, confounding, and statistical analysis/reporting; L, M, and H denote low, moderate, and high risk. Confounding and attrition were the main concerns.

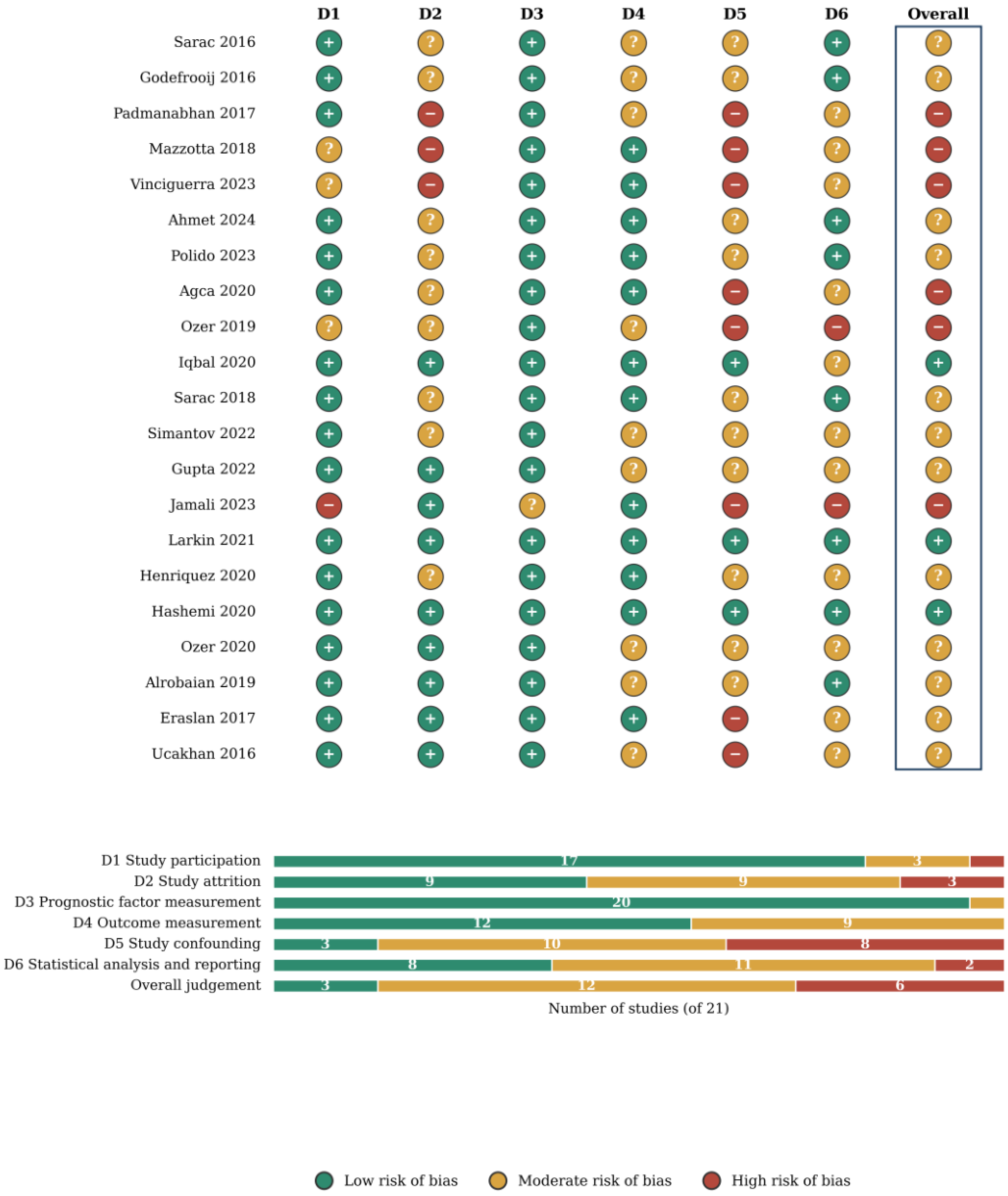


Figure 1. Risk of bias of the 21 included studies assessed with QUIPS

The evidence characteristics establish a methodological foundation for examining recurrent progression as a multidimensional clinical outcome rather than as a single homogeneous treatment failure event. Differences in study populations, protocol allocation, observation duration, and progression definitions restrict the interpretability of unstratified comparisons, particularly when studies employ different keratometric or tomographic criteria. The heterogeneity identified in earlier pooled research indicates that average failure estimates should be interpreted alongside the methodological and clinical characteristics from which they were derived (Achiron et al., 2022; Vinciguerra et al., 2023). The retained evidence consequently supports a narrative analytical approach that preserves study-specific definitions, distinguishes follow-up horizons, and evaluates prognostic associations according to the quality and comparability of the underlying clinical investigations.

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Long-Term Treatment Failure, Re-Progression, and Subsequent Surgical Intervention Following Pediatric Corneal Cross-Linking

The evaluation of postoperative keratoconus progression demonstrated substantial variation in reported treatment failure across different follow-up periods, cross-linking protocols, and outcome assessment criteria. Short-term investigations generally documented satisfactory stabilization after conventional epithelium-off treatment, whereas longer observation periods revealed that recurrent progression remained clinically relevant several years after the original intervention. The randomized KERALINK trial reported progression in 2 of 30 cross-linked eyes at 18 months, compared with 12 of 28 eyes receiving standard care, supporting the effectiveness of early intervention without establishing permanent postoperative stability (Larkin et al., 2021). These findings indicate that treatment efficacy and treatment durability represent related but distinct clinical outcomes, requiring separate consideration when evaluating the long-term prognosis of pediatric keratoconus.

During the initial 12–24 months of postoperative observation, reported failure rates ranged from 0% to 28.4%, with the widest differences occurring between treatment protocols rather than between conventional epithelium-off cohorts. A multicenter randomized trial identified no progression following standard epithelium-off CXL, compared with 5.4% after accelerated treatment and 28.4% following transepithelial intervention, suggesting that preservation of the corneal epithelium may reduce treatment effectiveness under the protocols investigated (Iqbal et al., 2020). A comparative cohort reported progression rates of 13.1% and 16.3% following standard and accelerated epithelium-off procedures, respectively, without a statistically significant difference between these treatment approaches (Sarac et al., 2018). The divergence between randomized and observational results indicates that protocol-specific failure rates require interpretation alongside treatment allocation, baseline corneal characteristics, and the criteria employed to define postoperative deterioration.

Intermediate follow-up investigations extending from three to five years demonstrated that corneal stabilization could be maintained in many patients, although the frequency of recurrent progression varied between clinical populations. A prospective Dutch cohort reported progression in 12 of 54 eyes, corresponding to 22%, whereas a separate prospective investigation involving 40 eyes documented no progression during 48 months of observation (Godefrooij et al., 2016; Uçakhan et al., 2016). Comparative evidence also identified progression in 9.37% of transepithelial-treated eyes after five years, compared with no progression among eyes receiving conventional epithelium-off treatment (Henriquez et al., 2020). The coexistence of stable and progressively deteriorating cohorts indicates that postoperative outcomes cannot be explained by follow-up duration alone, particularly when treatment protocols, disease severity, and progression thresholds vary between investigations.

Long-term observation extending beyond seven years provided additional evidence that recurrent progression may emerge after an initially satisfactory response to cross-linking. A ten-year cohort involving 175 eyes documented re-progression in 16 eyes, corresponding to 9.14%, while another ten-year investigation reported a failure rate of 24% using a definition incorporating keratometric deterioration or subsequent corneal transplantation (Ahmet et al., 2024; Mazzotta et al., 2018). A separate longitudinal cohort followed for a mean of 11.6 years reported substantially different failure frequencies depending on whether composite ABCD progression parameters or anterior curvature changes were applied (Vinciguerra et al., 2023). These findings suggest that reported long-term failure reflects the interaction between postoperative disease behavior and the measurement framework used to identify clinically meaningful deterioration.

Table 4 presents concise study-specific progression estimates by follow-up horizon, preserving denominators and comparisons that directly inform treatment failure. A dash denotes an outcome not reported; the 194-eye denominator for Padmanabhan et al. refers to observations beyond two years. These heterogeneous percentages are descriptive rather than a pooled effect.

Table 4. Reported Failure, Retreatment and Keratoplasty After Cross-Linking By Follow-Up Horizon

Follow-up	Study (eyes)	Failure / progression	Further intervention
12–24 mo	Larkin 2021 (30 CXL)	2/30 (7%); K2 ≥1.5 D	—
12–24 mo	Iqbal 2020 (271)	0% standard; 5.4% accelerated; 28.4% epi-on	—
12–24 mo	Sarac 2018 (87)	13.1% standard; 16.3% accelerated (P=.754)	—
12–24 mo	Hashemi 2020 (54)	3 accelerated vs 0 standard	None
12–24 mo	Ozer 2020 (41)	35% age ≤14 vs 4% age 15–18 (P=.014)	—
12–24 mo	Alrobaian 2019 (89)	18.5% vs 16.7% (P=.83)	—
12–24 mo	Eraslan 2017 (36)	5.6% epi-off vs 33.4% epi-on	—
3–5 y	Godefrooij 2016 (54)	12/54 (22%)	—
3–5 y	Ağca 2020 (143)	23.3% vs 16.8% (P=.411)	—
3–5 y	Ozer 2019 (35)	20%	—
3–5 y	Henriquez 2020 (78)	9.37% epi-on vs 0% epi-off	—
3–5 y	Uçakhan 2016 (40)	0/40	None
≥7 y	Padmanabhan 2017 (194*)	15% at 2 y; 24% after 4 y	—
≥7 y	Polido 2023 (74)	1.4%–14.6% across follow-up	—
≥7 y	Simantov 2022 (30 CXL)	3.33% CXL vs 26.6% untreated	1 repeat CXL
≥7 y	Mazzotta 2018 (62)	24%	2 grafts (3.2%)
≥7 y	Ahmet 2024 (175)	16/175 (9.14%)	3 repeats; 3 DALK (1.7% each)
≥7 y	Vinciguerra 2023 (38)	34% ABCD vs 7.9% anterior curvature	—
Retreated	Jamali 2023 (7)	Selected retreatment cohort	7 repeat CXL

Table 4 shows that re-progression is neither uniform nor restricted to the first postoperative years. Loss of Kmax stabilization increased from 15% at two years to 24% beyond four years in one large longitudinal cohort (Padmanabhan et al., 2017). Estimates across studies cannot be interpreted as a single incidence curve because follow-up completeness and progression thresholds differ.

The clinical significance of recurrent progression becomes more apparent when keratometric deterioration is distinguished from subsequent surgical intervention. Repeat cross-linking was required in 1 of 30 treated eyes during seven years of observation and in 3 of 175 eyes during a ten-year follow-up period, corresponding to reported retreatment frequencies of 3.33% and 1.7%, respectively (Simantov et al., 2022; Ahmet et al., 2024). Corneal transplantation was also documented in long-term cohorts, including 2 of 62 eyes undergoing grafting and 3 of 175 eyes requiring deep anterior lamellar keratoplasty (Mazzotta et al., 2018; Ahmet et al., 2024). These outcomes demonstrate that measurable re-progression and the requirement for additional surgical treatment constitute different levels of clinical severity, making their separate reporting essential for interpreting long-term treatment effectiveness.

The relatively low reported frequency of retreatment compared with tomographically defined progression indicates that crossing a numerical progression threshold does not necessarily result in immediate secondary intervention. A retrospective series of seven retreated pediatric eyes documented a mean interval of 49.71 months between primary and repeat cross-linking, illustrating that clinically significant deterioration requiring further treatment may develop several years after the initial procedure (Jamali et al., 2023). Retreatment decisions may also depend on the magnitude and persistence of anatomical deterioration, visual function, and the clinical assessment of progressive disease rather than isolated changes in a single tomographic parameter. The available evidence does

not establish a uniform threshold for repeat intervention, emphasizing the importance of distinguishing structural progression from management decisions when evaluating clinical endpoints.

The comparison between cross-linked and untreated fellow eyes provides additional information concerning the relative effectiveness of treatment despite the persistence of postoperative failure. A seven-year observational investigation reported deterioration requiring intervention in 8 of 30 untreated fellow eyes, whereas only one treated eye required repeat cross-linking during the same observation period (Simantov et al., 2022). Randomized evidence similarly demonstrated progression in approximately 7% of cross-linked eyes compared with 43% of eyes receiving standard care during an 18-month observation period (Larkin et al., 2021). These findings support the interpretation that recurrent progression following cross-linking represents a residual treatment risk rather than evidence that the intervention lacks clinical effectiveness, particularly when outcomes are compared against the natural course of untreated pediatric keratoconus.

Variation in the operational definition of postoperative progression represents a substantial limitation in comparisons of long-term CXL outcomes. The application of different ABCD-based criteria to the same 38-eye cohort produced progression estimates of 34% and 7.9%, demonstrating that outcome classification can generate differences exceeding those associated with several individual clinical characteristics (Vinciguerra et al., 2023). Other investigations employed thresholds of 1.0 or 1.5 diopters applied to maximum, mean, steep, or zonal keratometry, creating additional differences in the anatomical changes considered sufficient to establish treatment failure (Larkin et al., 2021; Hashemi et al., 2020; Polido et al., 2023). The available findings consequently support an interpretation of treatment durability that considers follow-up duration, protocol characteristics, progression criteria, and clinically consequential endpoints as separate analytical dimensions, while recognizing that standardized pediatric post-CXL progression criteria remain necessary for more reliable future comparisons.

Clinical, Tomographic, and Treatment-Related Predictors of Keratoconus Re-Progression Following Pediatric Corneal Cross-Linking

The identification of prognostic factors associated with recurrent keratoconus progression following pediatric corneal cross-linking revealed considerable differences in the consistency and strength of available clinical evidence. Treatment-related characteristics demonstrated more reproducible associations with postoperative failure than several baseline demographic and anatomical variables, particularly when comparisons involved epithelial removal and transepithelial procedures. Randomized evidence identified progression rates of 28.4% following transepithelial treatment, compared with 5.4% after accelerated epithelium-off cross-linking and no progression following conventional epithelium-off treatment (Iqbal et al., 2020). This pattern suggests that procedural characteristics affecting stromal treatment delivery may influence the durability of stabilization, although the interpretation of individual patient-level predictors remains constrained by differences in baseline disease severity and analytical adjustment.

The status of the corneal epithelium emerged as the most consistently supported treatment-related determinant of postoperative progression across the comparative investigations. A five-year prospective study documented progression in 9.37% of eyes receiving transepithelial cross-linking, whereas no progression was observed in the conventional epithelium-off group, indicating a persistent difference in treatment outcomes beyond the initial postoperative period (Henriquez et al., 2020). A separate comparative investigation reported stabilization or regression in 94.4% of epithelium-off eyes compared with 66.6% of epithelium-on eyes, further supporting the relevance of epithelial status to treatment effectiveness (Eraslan et al., 2017). The biological plausibility of this association relates to the barrier function of intact corneal epithelium, which may restrict riboflavin penetration and reduce the depth or distribution of stromal cross-link formation, although the observed clinical associations should not be interpreted as direct measurements of these mechanisms.

Differences between conventional and accelerated epithelium-off protocols were less consistent than those involving epithelial preservation, indicating that treatment acceleration cannot be classified as an independent determinant of failure on the basis of the available evidence. Comparative observational studies reported progression rates of 13.1% versus 16.3% for conventional and accelerated treatment and 23.3% versus 16.8% between two accelerated irradiation protocols, with neither comparison demonstrating a statistically significant difference (Sarac et al., 2018; Ağca et al.,

2020). Randomized evidence nevertheless identified some progression following accelerated treatment but none following conventional treatment, while a contralateral-eye trial involving patients with Down syndrome reported three early failures in the accelerated group and none in the standard-treatment group (Iqbal et al., 2020; Hashemi et al., 2020). These discrepancies indicate that irradiation intensity, treatment duration, and patient-specific corneal characteristics may interact in determining treatment response, but existing comparisons remain insufficient to establish a universal hierarchy among epithelium-off protocols.

Corneal thickness and cone location represented the most consistent anatomical predictors associated with postoperative progression, although their evidentiary strength remained limited by the number of studies reporting quantitative associations. An investigation using predefined tomographic thresholds identified a thinnest corneal thickness below 450 µm as associated with increased progression odds, with an odds ratio of 4.54 and a 95% confidence interval of 1.46–14.14, while paracentral cone location was associated with an odds ratio of 3.21 and a 95% confidence interval of 1.17–8.72 (Sarac et al., 2016). Additional evidence identified more decentered cones among progressing eyes and greater postoperative flattening in centrally located cones, supporting the possibility that cone position influences the distribution and effectiveness of treatment-induced biomechanical reinforcement (Godefrooij et al., 2016; Padmanabhan et al., 2017). The comparative patterns of treatment-related and patient-specific prognostic characteristics are presented in Table 5, retaining the original evidence classifications, quantitative findings, and assessments of consistency across studies.

Table 5. Synthesis of Candidate Predictors of Failure After Paediatric Cross-Linking

Predictor domain	Studies	Main quantitative signal	Interpretation
Epithelial status	Iqbal; Henriquez; Eraslan; Larkin	Epi-on 28.4% vs 0% standard at 2 y (Iqbal)	Consistently higher failure after epi-on
Epi-off irradiation	Sarac; Ağca; Iqbal; Hashemi	13.1% vs 16.3% (P=.754); 23.3% vs 16.8% (P=.411)	Inconsistent
Thinnest pachymetry	Sarac; Ozer	<450 µm: OR 4.54 (95% CI 1.46–14.14)	Suggestive; imprecise
Cone location	Sarac; Godefrooij; Padmanabhan	Paracentral: OR 3.21 (95% CI 1.17–8.72)	Consistent direction
Younger age	Ozer; Mazzotta; Jamali; Ahmet; Sarac	≤14 y: 35% vs 4% (P=.014)	Five of six studies supportive
Baseline Kmax / stage	Jamali; Ozer; Ahmet; Padmanabhan; Sarac	Kmax >58 D suggested by retreatment series	Inconsistent; no adjusted estimate
Allergy / eye rubbing	Iqbal; Jamali; Alrobaian; Gupta	6/7 retreated eyes reported rubbing	Comparative findings null
Down syndrome	Hashemi	3 failures accelerated vs 0 standard	One trial; indirect
Sex	Sarac; Alrobaian	No significant association	Consistent null
Failure definition	Vinciguerra; Ahmet; Polido	34% ABCD vs 7.9% curvature (same cohort)	Substantial classification effect

Table 5 summarizes direction, key quantitative estimates, and cross-study consistency for the main candidate predictors. Its findings should be interpreted alongside the study-specific risk-of-bias judgments in Figure 1.

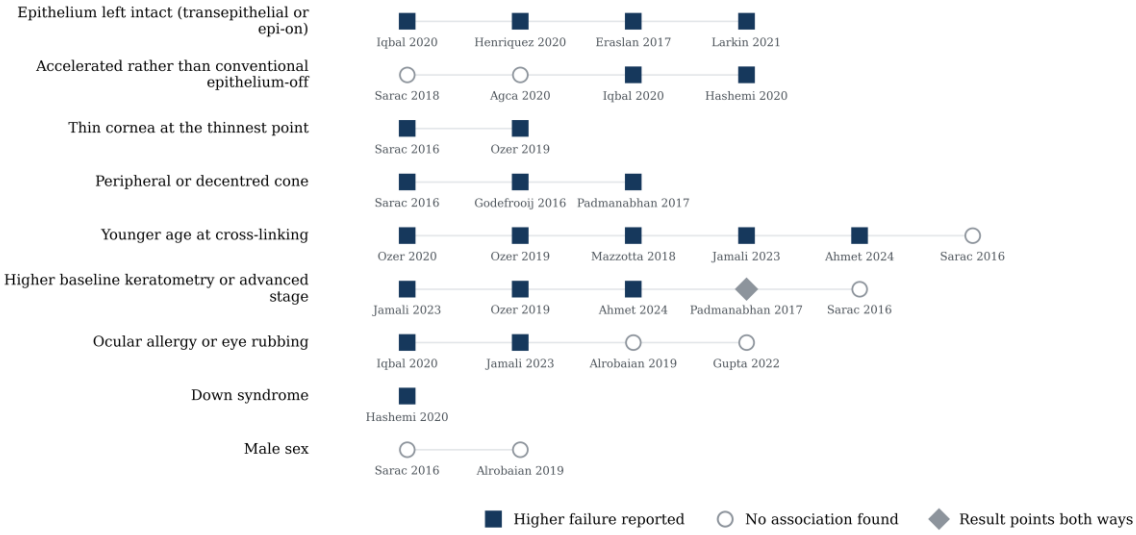


Figure 2. Direction of The Association Reported By Each Study, By Predictor Domain.

Age at cross-linking demonstrated a predominantly consistent association with subsequent progression, although the available findings did not establish whether chronological age independently determines treatment failure. A comparative cohort reported progression in 35% of eyes belonging to children aged 14 years or younger compared with 4% among patients aged 15–18 years, indicating a potentially substantial difference in postoperative stability between developmental groups (Ozer et al., 2020). Long-term observations similarly associated younger treatment age with recurrent progression, while another investigation did not identify a significant effect when patients were divided according to an age threshold of 14 years (Mazzotta et al., 2018; Sarac et al., 2016). The inconsistency may reflect correlations between younger age, corneal thickness, baseline disease severity, and cone morphology, making multivariable adjustment necessary before age can be interpreted as an independent prognostic determinant.

Baseline keratometric severity and ocular allergy presented less consistent associations with treatment failure, limiting their immediate application as isolated predictors of postoperative deterioration. A retrospective series involving retreated patients identified preoperative maximum keratometry above 58 diopters as a possible risk characteristic, whereas another investigation found no significant association between progression and a baseline maximum keratometry threshold of 54 diopters (Jamali et al., 2023; Sarac et al., 2016). Evidence concerning allergic disease showed a comparable discrepancy, with vernal keratoconjunctivitis frequently observed among progressing eyes but comparative analyses identifying no statistically significant difference between patients with and without allergic conditions (Iqbal et al., 2020; Alrobaian et al., 2019). These findings emphasize the methodological distinction between characteristics frequently observed among treatment failures and factors demonstrating an increased risk relative to an appropriate comparison population.

The interpretation of prognostic associations requires particular attention to confounding, outcome misclassification, and the limited availability of adjusted effect estimates. Most included investigations assessed individual characteristics through subgroup comparisons without adequately separating the contributions of age, baseline keratometric severity, corneal thickness, and cone position, despite the likelihood that these factors coexist in more advanced pediatric disease. The Quality in Prognosis Studies framework identifies confounding, prognostic factor measurement, and outcome assessment as distinct methodological domains, providing an appropriate basis for evaluating the credibility of reported associations (Hayden et al., 2013). The original assessment of evidence certainty is retained in Table 6, distinguishing the relatively stronger evidence concerning epithelial

status from patient-level predictors supported primarily by observational and methodologically heterogeneous investigations.

Table 6. GRADE Summary of Findings For Predictors of Failure After Paediatric Cross-Linking

Outcome / predictor	Studies (eyes)	GRADE certainty	Basis for judgment
Epi-on vs epi-off	4 (453)	Moderate	Consistent direction; randomized evidence; imprecision
Accelerated vs standard epi-off	4 (555)	Very low	Inconsistent comparisons; confounding
Thin cornea	2 (107)	Very low	Unadjusted estimates; serious imprecision
Decentered cone	3 (503)	Low	Consistent signal; residual confounding
Younger age	6 (422)	Very low	Inconsistent, largely unadjusted data
Baseline Kmax / stage	5 (761)	Very low	Conflicting results; no adjusted estimates
Allergy / eye rubbing	4 (483)	Very low	Descriptive signals vs null comparisons
Repeat CXL / keratoplasty	5 (364)	Low	Limited events; otherwise similar direction

Note to Table 6. Certainty incorporates study design, bias, inconsistency, indirectness, and imprecision; uncommon failures and small cohorts constrain most prognostic estimates.

The certainty assessment indicates that the direction of an observed association should not be equated with the reliability of the underlying prognostic evidence. As presented in Table 6, epithelial status received a moderate certainty rating because comparative findings demonstrated a consistent direction and included randomized evidence, whereas cone location received low certainty and several other patient-specific characteristics were supported by very-low-certainty evidence. The limited number of progression events, relatively small analytical populations, incomplete adjustment for confounding, and differences in outcome definitions substantially restricted the precision and comparability of prognostic estimates (Sarac et al., 2016; Godefrooij et al., 2016; Vinciguerra et al., 2023). These limitations indicate that treatment protocol, corneal thickness, cone centration, and younger age may inform clinical assessment, but their combined predictive performance remains unvalidated and cannot currently support a definitive individualized risk classification.

The clinical implications of these findings concern the selection of cross-linking techniques and the development of surveillance approaches proportionate to the characteristics of individual pediatric eyes. Epithelium-off treatment demonstrated more consistent stabilization than transepithelial procedures, while thinner corneas, decentered cones, and younger age were associated with less favorable postoperative outcomes across several investigations (Eraslan et al., 2017; Henriquez et al., 2020; Ozer et al., 2020). These associations support consideration of prolonged postoperative monitoring in patients with potentially unfavorable baseline characteristics, particularly because late progression may occur after several years of apparent stabilization. Further prognostic research requires adequately powered longitudinal cohorts, standardized postoperative progression criteria, and multivariable analyses capable of distinguishing independent predictors from correlated manifestations of advanced disease, thereby strengthening the evidentiary basis for personalized pediatric keratoconus management.

CONCLUSION

This systematic review demonstrates that corneal collagen cross-linking provides substantial protection against keratoconus progression in pediatric patients, although long-term stabilization is not achieved uniformly across treatment protocols and clinical populations. Evidence from 21 studies involving 1,967 eyes of 1,387 patients identified postoperative failure rates ranging from 0% to 28.4% during the first 12–24 months and from 9.1% to 34% in studies extending beyond seven years, with considerable variation attributable to differences in progression definitions and observation periods.

Treatment protocol emerged as the most consistent determinant of failure, with transepithelial and epithelium-on procedures demonstrating higher progression rates than conventional epithelium-off approaches, while accelerated epithelium-off treatment showed no consistently greater failure risk. Reduced corneal thickness, decentered cone location, and younger age were associated with increased susceptibility to postoperative deterioration, whereas baseline keratometry, ocular allergy, and eye rubbing did not demonstrate sufficiently consistent prognostic associations. Repeat cross-linking and keratoplasty were relatively uncommon, with reported frequencies of approximately 1.7%–3.3% and 1.7%–3.2%, respectively, in the relevant long-term cohorts. The certainty of evidence remained low to very low for most patient-level predictors, reflecting methodological limitations, inadequate adjustment for confounding, and heterogeneous outcome measurements.

The principal scientific contribution of this review lies in integrating long-term failure frequencies, treatment-related characteristics, patient-specific prognostic factors, and progression definitions into a structured assessment of pediatric CXL durability. The findings support the preferential consideration of epithelium-off protocols when clinically appropriate and indicate that patients with thinner corneas, decentered cones, or younger treatment age may benefit from prolonged postoperative surveillance extending beyond the second year. Clinical monitoring should incorporate multiple tomographic parameters rather than relying exclusively on maximum keratometry, particularly because different progression criteria can produce substantially different failure estimates within the same population. The available evidence does not justify a validated individualized prediction model or definitive risk thresholds for postoperative failure. Future investigations should prioritize standardized progression criteria, larger longitudinal cohorts, and multivariable prognostic analyses capable of distinguishing independent predictors from correlated clinical characteristics. These priorities would strengthen the reliability of risk assessment, improve the comparability of long-term treatment outcomes, and support more precise surveillance strategies for children and adolescents undergoing corneal collagen cross-linking.

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