A Detailed Phenotypic Characterization of Keratoconus in a Large Portuguese Cohort

Caracterização Fenotípica Detalhada do Queratocone numa Grande Coorte Portuguesa

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ABSTRACT

INTRODUCTION: Keratoconus (KC) is the most prevalent corneal ectatic disorder, defined by progressive thinning and steepening of the cornea. This study aims to provide a comprehensive phenotypic characterization of KC in a large Portuguese cohort, evaluating the correlation between disease severity, cone location, and clinical variables to enhance diagnostic accuracy and optimize treatment strategies.

METHODS: Cross-sectional study including patients diagnosed between 2018 and 2023 at two Portuguese ophthalmologic centers. A detailed analysis of corneal tomography was performed at baseline. These parameters were used to classify patients into five distinct phenotypic groups, considering cone location, anterior corneal curvature, and the alignment of topographic and comatic axes. Maximum keratometry (Kmax) for each patient was stratified across the four severity stages of the Amsler Krumeich classification. Associations between cone location, phenotype, and clinical parameters were assessed, including variations in age and corneal steepness across phenotypes.

RESULTS: A total of 411 eyes from 251 patients (65.9% male) were included. The mean baseline age was 23.14±5.20 years. The most prevalent keratoconus phenotypes were croissant (29.2%) and nipple (24.8%), followed by duck (20.0%), snowman (18.7%), and bowtie (7.3%). Patients with the snowman phenotype were significantly younger (21.00±6.43 years) than those with the croissant (23.83±4.15 years, p=0.002) and nipple (24.26±5.09 years, p<0.001) phenotypes. A significant association was found between keratoconus phenotype and sex (p=0.001), with males predominating in almost all phenotypes. The nipple phenotype was predominantly linked to advanced stages at presentation (81.2% at stage IV). Significant differences in keratometric values and corneal parameters were observed across phenotypes (p<0.001). Central cones, particularly those classified as nipple phenotype, were associated with steeper corneas and more severe disease at presentation.

CONCLUSION: The phenotypic distribution of keratoconus in this Portuguese population is consistent with findings from other cohorts, except for a higher prevalence of nipple type. Different keratoconus phenotypes were shown to correlate with clinical variables such as age,

sex, and disease severity. Central cones, especially the nipple phenotype, were linked to more severe disease at presentation and steeper corneas. These findings highlight the importance of phenotypic characterization in improving diagnostic accuracy and guiding treatment strategies for keratoconus.

KEYWORDS: Corneal Topography; Keratoconus/diagnosis; Keratoconus/genetics; Phenotype.

RESUMO

INTRODUÇÃO: O queratocone (QC) é ectasia corneana mais prevalente, definida por afinamento e aumento progressivo da curvatura da córnea. Este estudo tem como objetivo uma caraterização fenotípica detalhada do QC numa grande coorte portuguesa, avaliando a correlação entre gravidade da doença, localização do cone e variáveis clínicas, para melhorar a precisão diagnóstica e otimizar estratégias terapêuticas.

MÉTODOS: Estudo transversal incluindo doentes diagnosticados entre 2018 e 2023 em dois centros oftalmológicos portugueses. Realizou-se uma análise detalhada da tomografia corneana na avaliação inicial. Estes parâmetros foram utilizados para classificar os doentes em cinco grupos fenotípicos, considerando a localização do cone, curvatura anterior da córnea e alinhamento dos eixos topográfico e comático. Para cada doente, a gravidade da doença foi estratificada nos quatro estádios da classificação de Amsler Krumeich, de acordo com a queratometria máxima (Kmax). Avaliaram-se associações entre localização dos cones, fenótipo e parâmetros clínicos.

RESULTADOS: Foram incluídos 411 olhos de 251 doentes (65,9% do sexo masculino). A idade média inicial foi 23,14±5,20 anos. Os fenótipos mais prevalentes foram o *croissant* (29,2%) e o *nipple* (24,8%), seguidos do *duck* (20,0%), do *snowman* (18,7%) e do *bowtie* (7,3%). Os doentes com fenótipo *snowman* eram significativamente mais jovens (21,00±6,43 anos) do que aqueles com os fenótipos *croissant* (23,83±4,15 anos, p=0,002) e *nipple* (24,26±5,09 anos, p<0,001). Observou-se uma associação significativa entre fenótipo e sexo (p=0,001), com predomínio do sexo masculino em quase todos os fenótipos. O fenótipo *nipple* foi predominantemente associado a estádios avançados à apresentação (81,2% no estádio IV). Identificaram-se diferenças significativas nos valores queratométricos e parâmetros corneanos entre fenótipos (p<0,001). Cones centrais, particularmente os *nipple*, associaram-se a córneas mais curvas e maior gravidade da doença à apresentação.

CONCLUSÃO: A distribuição fenotípica do queratocone nesta população é consistente com os resultados de outras coortes, exceto pela maior prevalência do fenótipo *nipple*. Diferentes fenótipos correlacionam-se com variáveis clínicas como idade, sexo e gravidade da doença. Cones centrais, especialmente do fenótipo *nipple*, associaram-se a doença mais grave à apresentação e córneas mais curvas. Estes achados destacam a importância da caraterização fenotípica para melhorar a acuidade diagnóstica e orientar as estratégias de tratamento do queratocone.

PALAVRAS-CHAVE: Fenótipo; Queratocone/diagnóstico; Queratocone/genética; Topografia da Córnea.

INTRODUCTION

Keratoconus (KC) is a progressive ectatic disorder characterized by corneal thinning and steepening, resulting in irregular astigmatism and visual impairment. Keratoconus typically manifests in adolescence or early adulthood, making early detection crucial for effective management and improved long-term outcomes. However, early diagnosis is often complicated by the disease's subtle symptoms, which can mimic common refractive errors, leading to delays in diagnosis and treatment.[1] Clinical and phenotypical heterogeneity in KC also presents a significant challenge in clinical practice and research.

Keratoconus is often thought to be a common phenotypic presentation of different conditions or etiologies, rather than a single uniform disease. This conception is supported by the observation that KC can occur in association with a variety of systemic and genetic conditions, including connective tissue disorders such as Ehlers-Danlos syndrome, Marfan syndrome, and Down syndrome.[2,3] The variability in clinical presentation, progression rates, and response to treatment suggests that KC may represent a spectrum of dis-

orders with distinct underlying genetic and environmental factors contributing to the ectatic phenotype. This diversity in etiology and pathogenesis has led to the recognition that KC may not be a singular entity but rather a final common pathway resulting from multiple contributing mechanisms, including genetic predisposition, biochemical abnormalities, and environmental influences such as eye rubbing and atopy.[3,4] This has driven efforts to systematically classify KC features into well-defined, recognizable phenotypic groups.

Over the years, various classification systems have emerged to make sense of these phenotypical differences and categorize keratoconus based on features such as corneal morphology, disease progression, optical function, and corneal shape descriptors (index-based systems). Among these, the Amsler-Krumeich classification is one of the most widely used in clinical practice, focusing on morphological and clinical features.[1] Grading systems and phenotypic classifications can guide treatment decisions by identifying patients at different stages or different presentations of the disease who may benefit from specific therapeutic approaches. They also enable the identification of high-risk patients who require closer monitoring to prevent rapid progression and vision loss. These frameworks also help standardize the assessment of patients, enabling consistent communication between healthcare providers and facilitating the comparison of clinical outcomes across studies.

Classification systems focused on cone morphology and location have demonstrated significant utility in guiding the implantation of intrastromal corneal ring segments (ICRS) and predicting the outcomes of both ICRS and corneal collagen crosslinking (CXL) procedures.[5,6] The Fernández-Vega/Alfonso classification, for example, identifies five distinct phenotypes based on corneal morphology and topographic astigmatism: *croissant*, *duck*, *snowman*, *nipple*, and *bowtie*. This classification has significant therapeutic and prognostic implications.[7]

Recognizing the common presentations of keratoconus within a population is essential for enhancing diagnostic accuracy and refining treatment strategies. In this study, we aim to conduct a comprehensive phenotypic characterization of KC in a large cohort of Portuguese patients. By analyzing clinical, topographic, and tomographic data, we seek to identify prevalent patterns and investigate potential correlations between phenotypes and disease severity, facilitating patient care, improving outcomes and paving the way for future research.

METHODS

STUDY DESIGN

This cross-sectional study was carried out at two ophthalmology centers in Portugal. Approval from the ethical committees of both institutions was obtained. The study followed the tenets of the Declaration of Helsinki.

PATIENTS

A comprehensive list of keratoconus patients diagnosed between 2018 and 2023 at both centers was compiled through a targeted keyword search in electronic medical records and data exports from corneal tomography systems. A standardized evaluation protocol was applied at both centers, ensuring uniformity in the diagnostic process and clinical data collection for all patients. Keratoconus diagnosis was made in accordance with the Global Consensus on Keratoconus and Ectatic Diseases guidelines.[3] Patients with a history of ocular surgeries, prior keratoconus treatments, or other corneal or ocular conditions were excluded from the study. A detailed clinical database was then created, including demographic information and baseline corneal tomography parameters for each patient.

CONE LOCATION CLASSIFICATION

Cone classification was based on the location of the thinnest corneal point and Kmax as measured by baseline Pentacam.

According to thinnest point, cones were classified as central if both coordinates were less than 0.8 mm, paracentral if one or both were equal or above 0.8 mm and under 1.6 mm, and pericentral if one or both were 1.6 mm or greater.[8]

Based on Kmax, a cone was classified as central if the Kmax was located within the central 3 mm zone. If the Kmax fell between 3.01 mm and 5 mm, the cone was defined as paracentral, and if located beyond the 5 mm zone, the cone was considered peripheral.[5,9,10]

Cases with pericentral and peripheral cones, potentially associated with pellucid marginal degeneration,[5] were excluded. Ungradable cases, both due to very early or very advanced disease, were also excluded.

For each patient, Kmax was stratified across the four severity stages of the Amsler Krumeich classification.

PHENOTYPE CLASSIFICATION

Phenotypic classification was performed by two independent graders, one from each center, and any discrepancies in classification were resolved by a third corneal specialist.

Patients were categorized into five phenotypes based on cone location, topographic astigmatism patterns, corneal asphericity, and the alignment of the topographic, refractive, and comatic axes.

The *croissant* phenotype is defined by a paracentral or pericentral cone where the topographic and refractive axes are closely aligned (within 30º), often presenting as a "crab claw" pattern on the curvature maps.

The *duck* phenotype represents a paracentral cone with moderate misalignment between the topographic and comatic axes (ranging from 30º to 59º), creating asymmetrical angulated lobes in the axial or tangential anterior curvature maps.

The *snowman* phenotype is a paracentral keratoconus where the topographic and comatic axes are nearly perpendicular (60º-120º), resulting in asymmetrical non-angulated lobes on the curvature maps.

The *nipple* phenotype is a central cone with high corneal asphericity (Q<-1.25), often depicted on axial and tangential maps as a central bull's-eye with a prominent steep elevation, commonly referred to as a "red island."

Lastly, the *bowtie* phenotype involves a centrally located

cone with lower asphericity (Q>-1.25) and regular astigmatism, with the topographic and refractive axes remaining closely aligned within 30º, creating a symmetric bowtie-like shape in the curvature maps.

STATISTICAL ANALYSIS

Statistical analysis was conducted using IBM SPSS Statistics® for Windows (version 29).

The demographic and clinical characteristics of the cohort were summarized using means, standard deviations, and frequencies to provide a comprehensive overview of the study population. Cohen's kappa (κ) was calculated to assess the level of agreement between the two graders in phenotypic classification. Chi-square tests were performed to assess the association between keratoconus phenotypes and sex. A post-hoc analysis was carried out to compare age differences among phenotypes, employing pairwise comparisons to identify significant variations between groups. A one-way ANOVA was used to evaluate differences in keratometric values (Km and Kmax) across the various keratoconus phenotypes. Additionally, a correlation analysis was conducted to investigate associations between cone location and disease severity. Statistical significance was defined as a *p*-value under 0.05.

RESULTS

A total of 411 eyes from 251 patients were included in the study, with 49.4% (n=203) being right eyes. Cases were collected from two ophthalmology centers, with 87.8% (n=361) of eyes from one center and 12.2% (n=50) from the other. Most patients were male (65.9%, n=165), with females comprising 34.1% (n=86). The mean baseline age was 23.14 ± 5.20 years. Fifty-two patients (12.65%) were younger than 18 years old. The detailed characterization of the tomographic features of our cohort is outlined in Table 1.

Table 1. Baseline tomographic characterization of the cohort.

Corneal tomography parameter	Mean ± SD
Km, D	47.40 ± 5.52
Kmax, D	55.47 ± 7.97
Thinnest pachymetry, μm	468.35 ± 41.11
ARC, mm	6.74 ± 0.71
A	2.52 ± 2.20
PRC, mm	5.09 ± 0.70
B	3.85 ± 2.77
C	1.64 ± 0.87
BAD-D	9.52 ± 21.12

D: diopters; K: keratometry; Km: average keratometry; Kmax: maximum keratometry; ARC: anterior radius of curvature of a 3 mm zone centered on the thinnest point of the cornea; PRC: posterior radius of curvature of a 3mm zone centered on the thinnest point of the cornea; ABC: ABCD Grading System; BAD-D: Belin/Ambrósio Enhanced Ectasia Display.

CONE LOCATION

According to maximum keratometry location, 61.3% (n=252) of cases were considered central, while 38.7% (n=159) were paracentral. No cases were classified as peripheral. Based on the thinnest corneal point, 73.0% (n=300) were classified as central and 27.0% (n=111) as paracentral, with no peripheral cases noted.

PHENOTYPE CLASSIFICATION

The most prevalent keratoconus phenotype was *croissant*, observed in 29.2% (n=120) of the eyes, followed by the *nipple* in 24.8% (n=102). The *duck* phenotype was present in 20.0% (n=82) of the eyes and 18.7% (n=77) exhibited a *snowman* phenotype. The *bowtie* had the lowest prevalence, accounting for 7.3% (n=30) of cases. Inter-grader agreement for phenotype classification was considered almost perfect (κ = 0.837). Table 2 provides a summary and comparison of the baseline characteristics for the five keratoconus phenotypes.

SEVERITY STAGING

Using the Amsler-Krumeich classification, the distribution of keratoconus stages revealed a predominance of advanced disease at baseline. Stage I keratoconus was observed in 16.5% (n=68) of the patients, while 26.0% (n=107) were classified as stage II. A smaller proportion, 8.8% (n=36), were in stage III. Notably, the largest group, comprising 48.2% of patients (n=198), presented with the most severe form of keratoconus, classified as stage IV. In the pediatric group of our cohort, keratoconus severity was classified as stage I in 17.3% (n=9) of patients, stage II in 23.1% (n=12), stage III in 7.7% (n=4), and stage IV in 51.9% (n=27).

CLINICAL INSIGHTS

There was significant variability in keratoconus severity across phenotypes ($p<0.001$), with the *croissant*, *duck*, and *nipple* phenotypes predominantly presenting with more severe disease. Notably, among the patients with the *nipple* phenotype, 81.2% were at stage IV at presentation.

A significant association was found between keratoconus phenotype and sex ($p=0.001$), with males predominating in almost all phenotypes, consistent with the overall study population. The *bowtie* phenotype was an exception, displaying a nearly equal distribution between sexes.

A post-hoc analysis assessed age differences among patients with various keratoconus phenotypes, revealing that patients with the snowman phenotype, with a mean age of 21.00±6.43 years, were significantly younger than those with the *croissant* (23.83±4.15 years, $p=0.002$), and the *nipple* phenotype (24.26±5.09 years, $p<0.001$). This finding suggests that certain phenotypes, such as the *snowman*, are likely to manifest earlier in life.

Cone location, determined by either the site of maximum keratometry or the thinnest corneal point, significantly correlated with the severity of keratoconus at presentation. Central cones were linked to more advanced forms of keratoconus ($p<0.001$), indicating a correlation between cone location and disease severity at diagnosis.

A one-way ANOVA revealed significant differences in Km and Kmax values across phenotypes ($p<0.001$), supporting the relationship between cone location and corneal steepness. Central cones, particularly those clas-

Table 2. **Baseline characteristics of each phenotypic group.**

	Disease Phenotype *					
	1 "croissant" 29.2% (n=120)	**2 "duck"** 20.0% (n=82)	**3 "snowman"** 18.7% (n=77)	**4 "nipple"** 24.8% (n=102)	**5 "bowtie"** 7.3% (n=30)	*p*
Age at baseline, years	23.83±4.15	22.79±4.93	21.00±6.43	24.26±5.09	22.97±5.14	<0.001
Km, D	45.50±5.53	46.02±3.00	46.06±3.54	51.89±6.18	47.02±4.24	<0.001
Kmax, D	54.78±6.58	52.80±5.60	52.56±6.58	61.70±8.78	52.01±7.67	<0.001
Thinnest pachymetry, µm	472.18±37.74	479.80±32.67	481±39.93	440.82±37.45	481.13±47.48	<0.001
ARC, mm	6.74±0.66	7.02±0.52	7.11±0.57	6.15±0.60	7.08±0.67	<0.001
A	2.52±1.88	1.67±1.29	1.52±1.58	4.32±2.57	1.63±1.88	<0.001
PRC, mm	5.06±0.64	5.34±0.54	5.47±0.60	4.50±0.56	5.54±0.62	<0.001
B	3.89±2.49	2.93±1.99	2.43±2.02	6.30±2.79	2.35±2.15	<0.001
C	1.59±0.85	1.36±0.70	1.42±0.88	2.11±0.71	1.51±1.20	<0.001
BAD-D	12.60±39.37	6.33±2.84	5.51±3.40	12.57±5.91	4.19±3.40	<0.001

. Baseline characteristics of all 5 disease phenotypes, including one-way ANOVA comparison between groups. D: diopters; K: keratometry; Km: average keratometry; Kmax: maximum keratometry; ARC: anterior radius of curvature of a 3 mm zone centered on the thinnest point of the cornea; PRC: posterior radius of curvature of a 3 mm zone centered on the thinnest point of the cornea; ABC: ABCD Grading System; BAD-D: Belin/Ambrósio Enhanced Ectasia Display.

sified as *nipple* phenotype, were associated with steeper corneas (Fig. 1).

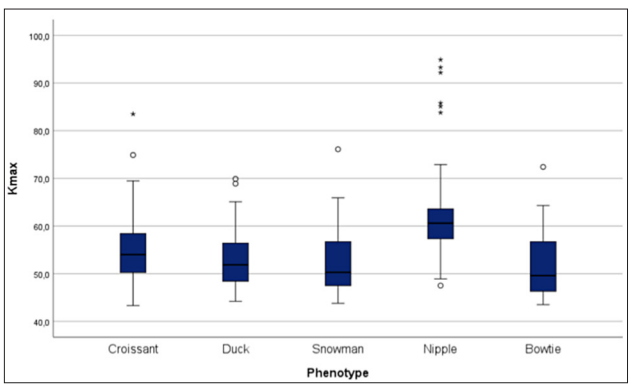

Figure 1. Distribution of maximum keratometry values (Kmax) across different keratoconus phenotypes.

The *nipple* phenotype demonstrates the steepest corneas, with the highest median Kmax and the greatest variability, while the *bowtie* phenotype shows lower median Kmax values, suggesting milder keratoconus.

DISCUSSION

In this study, we characterized the phenotypic and demographic features of a large cohort of keratoconus patients, emphasizing the association between phenotype, disease severity, and cone location. Our findings underscore the variability that can be found in the clinical presentation and treatment alternatives in KC and highlight the importance of knowing in detail how the condition presents in our specific population. To the best of our knowledge, this is the largest cohort of Portuguese keratoconus patients ever published. Outlining the actual features of the patients we are tasked with treating can help us provide more accurate diagnosis, more suitable follow-up regimens, and more personalized treatment options.

In our cohort, central cones, defined by maximum keratometry or thinnest corneal pachymetry, were most frequently observed. Consistent with previous studies,[11,12] we observed that central cones, particularly those linked to the *nipple* phenotype, tend to be associated with steeper corneas. The focal corneal thinning and steepening characteristic of keratoconus is often attributed to localized, not generalized, biomechanical weakening.[13,14] The biomechanical properties of central cones may differ from those of paracentral cones, potentially contributing to more pronounced protrusion and increased steepness.[15]

We found a significant correlation between cone location and disease severity, with central cones being associated with more advanced keratoconus at presentation. Other studies have similarly highlighted the critical role of cone location in assessing keratoconus severity.[16,17] Eliasy *et al* examined 309 keratoconus patients and demonstrated that a shorter distance from the cone center to the corneal vertex correlates with increased disease severity.[17]

The predominance of stage IV patients in our cohort is particularly meaningful in how it reveals a gap in our current ability to screen and treat patients at an earlier stage. In the current context of KC treatment, where crosslinking has consistently shown to be an efficient tool to control progression, identifying patients at risk of progression is of paramount importance. It is known that patients with steeper keratometry at presentation have a higher risk of progression, and thus of needing CXL.[18] Also, pediatric patients, those most likely to perform CXL, also tend to present with more advanced KC cases than adults.[19,20] In the pediatric subgroup of our cohort, the majority of patients presented with stage IV keratoconus, emphasizing the increased prevalence of advanced

disease in younger populations. Given that our cohort is likely representative of the broader Portuguese keratoconus population, these results emphasize the need for improved screening programs and timely intervention to enhance patient outcomes. Furthermore, the correlation between the nipple phenotype and steeper cones that we have mentioned is in line with the known literature, but, once again, highlights the importance of tailoring keratoconus care having the distinct phenotype of each patient in mind.

Our findings reinforce the need for tailored care for patients with different phenotypical presentations, namely for patients with central cones. With effective interventions, such as CXL, available to halt disease progression, early identification of these high-risk phenotypes is crucial. These patients would benefit from closer monitoring and timely intervention to prevent severe visual impairment. By recognizing and prioritizing high-risk phenotypes, clinicians can enhance patient outcomes and quality of life, demonstrating the importance of phenotype-based personalized management.

Morphological or phenotypic segmentation can also play a crucial role in determining the most suitable treatment protocol for keratoconus patients. In conventional CXL protocols, UVA light is applied centrally along the visual axis, which leads to reduced treatment intensity and a weaker crosslinking effect in the peripheral cornea.[10] Consequently, central cones tend to exhibit more pronounced flattening and greater improvements in refractive errors[5,9] and spherical aberrations.[10] On the other hand, patients with peripheral or paracentral cones may benefit from customized CXL approaches that ensure effective treatment across the entire corneal surface. Similar to the tailored approach used for intracorneal ring segment implantation, incorporating cone location into pre-treatment evaluations can help clinicians develop more personalized treatment plans, ultimately improving long-term outcomes for keratoconus patients.

In terms of phenotype distribution, croissant phenotype was the most prevalent in our cohort, followed by the *nipple* and *duck* phenotypes. The observed distribution aligns with reports from previous studies,[7] except for a higher prevalence of *nipple* phenotype. This increased prevalence may be attributed to genetic, environmental, or demographic factors unique to our population.

Our post-hoc analysis revealed significant age differences across phenotypes, with the *snowman* phenotype presenting in younger patients compared to both the *croissant* and *nipple* phenotypes. This suggests that certain phenotypes, such as the *snowman*, may manifest earlier in life, which could have implications for screening and monitoring strategies in younger patients. Early identification of phenotypes associated with younger age could allow for timely intervention, potentially halting disease progression before severe corneal changes occur.

Our study has some limitations. While we benefit from a large sample size, it is restricted to two ophthalmology centers in Portugal, which may limit the generalizability of our findings to other populations. It is also important to note that we did not collect data on patients' ethnic backgrounds. Both centers included in this study serve as referral points for severe cases from other countries with established protocols with the Portuguese National Health System, particularly from Portuguese-speaking African countries (PALOP). This may represent a confounding factor influencing the characterization of our sample, as these patients typically present with more severe and advanced keratoconus. There were also limitations inherent to the phenotypic classification process, as there was not full concordance between the two graders. Nonetheless, perfect agreement is rarely achieved in these contexts. Variability can arise from subtle differences in clinical judgment, experience, or interpretation of borderline cases, particularly for intermediate or atypical phenotypes. The involvement of a third experienced grader to resolve these rare discrepancies was crucial in minimizing the impact of this variability. Finally, the retrospective and cross-sectional design of our study prevents us from evaluating disease progression over time.

In conclusion, this study reveals strong associations between cone location, phenotype, and keratoconus severity, offering valuable insights for clinical practice. To the best of our knowledge this is the most comprehensive characterization of a keratoconus cohort ever published on a Portuguese population. It provides an invaluable opportunity for a clear view at the actual phenotypical presentation of keratoconus in the Portuguese context. Our findings emphasize the importance of integrating phenotypic characterization into clinical evaluations to enhance personalized treatment strategies and improve patient outcomes. Even more important, this study lays the groundwork for future research to validate these associations across diverse populations and refine therapeutic approaches for keratoconus patients. These findings pave the way for a more nuanced understanding of keratoconus, its clinical features, progression profile and response to treatments. By incorporating these phenotypic factors into clinical algorithms, we can improve the accuracy of progression predictions and guide more effective, individualized treatment strategies. Hopefully, future research can aim to validate these findings in broader populations and develop refined, phenotype-specific therapeutic approaches to enhance patient care.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

MF: Conceptualization, formal analysis, data collection, writing the manuscript.

JG, PG: Conceptualization, formal analysis, writing –

review and editing.

NA, JF, EC, AR, CT, MJQ, JM: Critical revision.

All authors approved the final version to be published.

MF: Conceptualização, análise formal, recolha de dados, redação do manuscrito.

JG, PG: Conceptualização, análise formal, redação – revisão e edição.

NA, JF, EC, AR, CT, MJQ, JM: Revisão crítica.

Todos os autores aprovaram a versão final a ser publicada.

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

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