# Corneal Cross-Linking and Transplantation Trends for Keratoconus in Portugal: A Multicenter Retrospective Analysis

# Tendências do *Cross-Linking* e Transplantes de Córnea por Queratocone em Portugal: Uma Análise Retrospectiva Multicêntrica

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## ABSTRACT

**INTRODUCTION:** Keratoconus (KC) is a corneal ectatic disorder characterized by progressive thinning and protrusion. Approximately 20% of KC patients eventually require corneal transplantation. Corneal cross-linking (CXL) has proven effective in halting disease progression, potentially preventing or delaying the need for transplantation. This study aims to evaluate whether current patterns of CXL implementation have impacted the number of corneal transplants in KC patients in Portugal.

**METHODS:** Multicentric retrospective study conducted at three Portuguese tertiary centers. Data regarding corneal transplantations performed between 2011 and 2024 were collected from the Eye Bank registries of the participating centers. Data on CXL procedures performed during the same period were retrieved from medical records. Temporal trends in corneal transplantation were analyzed in relation to the introduction and subsequent adoption of CXL.

**RESULTS:** Between 2011 and 2024, a total of 5595 corneal transplants were performed across the three centers. Of these, 864 (15.4%) were for KC, including 542 (62.7%) penetrating keratoplasties (PK) and 322 (37.3%) deep anterior lamellar keratoplasties (DALK). During the same period, 397 CXL were performed. Patients undergoing CXL were significantly younger than those receiving keratoplasty (21.1 ± 2.5 *vs* 34.9 ± 2.1 years, $p< 0.001$). Since 2018, the annual number of CXL procedures increased significantly (7.3 ± 6.1 to 49.4 ± 12.2, $p<0.001$), while transplants for KC showed a non-significant decline (64.7 ± 10.1 to 58.7 ± 16.5, $p=0.427$). No statistically significant association was found between CXL activity and keratoplasty rates, although a negative trend was observed. The proportion of CXL procedures relative to KC-related transplants increased significantly over time ($p<0.001$). Only one patient who underwent CXL subsequently required corneal transplantation.

**CONCLUSION:** CXL use has increased substantially in recent years, reinforcing its role as an effective treatment to halt KC progression. However, this wider availability has not yet translated

into a measurable reduction in the overall burden of KC requiring transplantation. Early diagnosis and intervention, as well as the standardization of follow-up and treatment guidelines, are essential to understand and enhance the preventive benefit of CXL at the healthcare system level.

**KEYWORDS:** Cornea; Corneal Cross-Linking; Corneal Transplantation; Keratoconus.

## RESUMO

**INTRODUÇÃO:** O queratocone (QC) é uma ectasia corneana caracterizada por afinamento e protrusão progressivos. Cerca de 20% dos doentes com QC necessitarão, eventualmente, de transplante de córnea. O *cross-linking* corneano (CXL) demonstrou ser eficaz em atrasar a progressão da doença, podendo prevenir ou adiar a necessidade de transplante. Este estudo tem como objetivo avaliar o impacto da implementação do CXL no número de transplantes de córnea em doentes com QC em Portugal.

**MÉTODOS:** Estudo retrospetivo multicêntrico realizado em três centros terciários portugueses. Foram recolhidos dados relativos aos transplantes de córnea realizados entre 2011 e 2024, a partir dos registos dos Bancos de Olhos dos centros participantes. Os dados sobre os CXL efetuados no mesmo período foram obtidos dos registos clínicos. Analisaram-se as tendências temporais e a relação entre transplantes e adoção do CXL.

**RESULTADOS:** Entre 2011 e 2024, foram realizados 5595 transplantes de córnea nos três centros. Destes, 864 (15,4%) foram por QC, incluindo 542 (62,7%) queratoplastias penetrantes (QP) e 322 (37,3%) queratoplastias lamelares anteriores profundas (DALK). No mesmo período, foram realizados 397 CXL. Os doentes submetidos a CXL eram significativamente mais jovens do que os submetidos a queratoplastia (21,1 ± 2,5 *vs* 34,9 ± 2,1 anos, $p<0,001$). Desde 2018, o número anual de CXL aumentou significativamente (7,3 ± 6,1 para 49,4 ± 12,2, $p<0,001$), enquanto os transplantes por QC apresentaram um decréscimo não significativo (64,7 ± 10,1 para 58,7 ± 16,5, $p=0,427$). O aumento do CXL não se associou a uma redução significativa dos transplantes por QC, apesar da tendência negativa observada. A proporção de CXL face aos transplantes por QC aumentou significativamente ($p<0,001$). Apenas um doente submetido a CXL necessitou posteriormente de transplante.

**CONCLUSÃO:** A utilização do CXL aumentou substancialmente nos últimos anos, reforçando o seu papel como tratamento eficaz para atrasar a progressão do QC. Contudo, em Portugal, esta maior disponibilidade ainda não se traduziu numa redução mensurável dos casos que requerem transplante. O diagnóstico e a intervenção precoces, bem como a uniformização das normas de seguimento e tratamento, são essenciais para potenciar o benefício preventivo do CXL nos sistemas de saúde.

**PALAVRAS-CHAVE:** Córnea; Crosslinking Corneano; Queratocone; Transplante de Córnea.

## INTRODUCTION

Keratoconus (KC) is the most prevalent corneal ectatic disorder, characterized by progressive thinning of the corneal stroma and localized protrusion, resulting in irregular astigmatism and significant visual impairment.[1] The global burden of KC is increasing, with an estimated incidence of 4.0 per 100 000 person-years and a prevalence of 289.1 per 100 000, affecting more than 23.7 million individuals worldwide.[2] Diagnosis is typically established at a young age, leading to a substantial impact on patients' quality of life and imposing a significant medical and socioeconomic burden.

KC treatment depends on disease severity and progression. For many years, management of mild and moderate cases relied on correction of the refractive errors through spectacles or rigid contact lenses. Despite this, KC is a progressive disease, and it has been estimated that up to 20% of patients will eventually require corneal transplantation.[3]

Corneal cross-linking (CXL) is a surgical technique that relies on the photoactivation of riboflavin through ultraviolet-A (UVA) light, to induce covalent bonds within the stromal collagen fibers. Thus, CXL increases the biomechanical stability and rigidity of the cornea and has proven effective in halting disease progression.[4–6] CXL was first described as a potential treatment for KC in 2003.[4] Since then, several modifications have been described to reduce the duration and improve the treatment efficiency. Long-term evidence has demonstrated efficacy, safety, and durability of disease stabilization and CXL is now globally accepted as a first-line treatment for progressive KC.[5–7]

By halting disease progression, CXL may reduce the proportion of patients progressing to advanced stages of KC and requiring keratoplasty. In Norway, a 50% decrease

in the rate of penetrating keratoplasty was observed in the 6 years after the implementation of CXL.[8] Three years after the introduction of CXL in Netherlands, there was a 25% reduction in transplant rates for KC.[9] In Canada, the proportion of keratoplasties performed for KC decreased after the CXL implementation, but the absolute number of keratoconus-related transplants remained unchanged.[10]

In Portugal, CXL has been progressively implemented over the past decade, but nationwide data on its impact on corneal transplantation remain limited. Despite international evidence, no studies have yet evaluated whether the introduction of CXL has modified the demand for keratoplasty in the Portuguese population. Understanding this relationship is crucial to optimize resource allocation and assess the long-term effectiveness of preventive interventions in keratoconus.

This study aims to evaluate temporal trends in corneal transplantation for KC in Portugal with the introduction and increasing use of CXL, to clarify the impact of CXL on the need for corneal grafting in this population.

# METHODS

## STUDY DESIGN

This retrospective multicenter study was carried out at three tertiary ophthalmology centers in Portugal (Centers A, B and C). The study followed the tenets of the Declaration of Helsinki.

## DATA COLLECTION

Data on all corneal transplants performed between January 2011 and December 2024 were collected from the Eye Bank registries of the three participating centers. All patients with a diagnosis of KC who underwent corneal transplantation during this period were identified. For each patient, we noted sex, age at the time of surgery, and the type of keratoplasty performed (penetrating keratoplasty [PK] or deep anterior lamellar keratoplasty [DALK]). Data on CXL procedures performed during the same period were retrieved from the medical records and surgical databases of the three centers. Indications for CXL and keratoplasty followed standard clinical practice and were not strictly protocolized within the scope of this study. For each patient, we recorded sex, age at the time of surgery, and whether corneal transplantation was further required.

## STATISTICAL ANALYSIS

Statistical analysis was conducted using IBM SPSS Statistics® for Windows (version 29). Quantitative variables were summarized as means and standard deviations and categorical variables as absolute numbers and percentages.

A repeated-measures ANOVA was applied to compare the number of corneal transplants and CXL procedures between centers. When overall significance was detected, pairwise comparisons were adjusted for multiple testing using the Bonferroni correction.

For temporal analysis, the study period was divided into a pre-CXL phase (2011–2017), during which only a limited number of procedures were performed, and a post-CXL phase (2018–2024), corresponding to the years of widespread adoption and increased use of CXL across the participating centers. Data regarding the average annual resident population in Portugal for each period were retrieved from the PORDATA database. Independent samples t-tests were performed to assess differences in the annual number of corneal transplants between the two periods.

Linear regression was used to assess temporal trends in the number of transplants for KC and to evaluate the association between the number of CXL procedures and the number of corneal transplants for KC. A segmented regression model was applied to analyze whether the relationship between CXL and keratoplasty differed between pre- and post-CXL periods.

To explore potential delayed effects of CXL, a lag correlation was performed between the number of transplants for KC in year n and the number of CXL procedures in prior years.

A $p$-value < 0.05 was considered statistically significant.

# RESULTS

Between 2011 and 2024, a total of 5595 corneal transplants were carried out across the three participating centers (A-C). Of these 864 (15.4%) were for KC, including 542 (62.7%) PK and 322 (37.3%) DALK. Among patients receiving transplants for KC, the majority were male (n= 533, 61.7%). During the same period, 397 CXL procedures were performed, involving 252 (63.5%) male and 145 (36.5%) female patients. Those undergoing CXL were significantly younger (21.1 ± 2.5 years old) than those undergoing corneal transplantation (34.9 ± 2.1 years old, $p$<0.001). Only one patient who underwent CXL later required a corneal transplant, 16 months after treatment. Data on corneal transplants and CXL procedures performed by center are summarized in Table 1.

Significant differences were found in the total number of corneal transplants between centers ($F_{(2,12)}$ = 8.30, $p$=0.005), with Center B showing the highest mean annual number of transplants (149.6 ± 7.3). Bonferroni-adjusted post hoc tests indicated that Center B performed significantly more transplants than Center A (119.2 ± 5.6; $p$=0.003), while the difference with Center C (130.8 ± 8.6; $p$=0.035) did not remain significant after Bonferroni correction. No difference was observed between Centers A and C ($p$=0.324).

When considering transplants performed specifically for KC, no significant differences were found across centers ($F_{(2,26)}$ = 0.90, $p$=0.42). The mean annual numbers were 21.9 ± 7.0 in Center A, 18.4 ± 5.7 in Center B, and 21.4 ± 9.6 in Center C. Regarding CXL procedures, significant differences were observed across the three centers ($F_{(2,26)}$ = 6.68, $p$=0.011), with a significantly higher number in Center A (16.6 ± 16.7) than in Centers B (6.0 ± 6.8, $p$=0.039) and C (5.7 ± 5.2, $p$=0.057). There was no significant difference between Centers B and C ($p$=1.000). Annual distributions of KC-related corneal transplants and CXL procedures by center, together with the overall temporal trends, are shown in Figs. 1 and 2, respectively.

In the combined dataset from the three centers, the first

**Table 1. Summary of corneal transplants and corneal cross-linking (CXL) procedures performed between 2011 and 2024 across the three participating centers (A–C).**

| | Center A | Center B | Center C | Total |
|---|---|---|---|---|
| Corneal transplants (total) | 1669 | 2095 | 1831 | 5595 |
| Corneal transplants for KC | 307 | 257 | 300 | 864 |
| PK | 199 | 223 | 120 | 542 |
| DALK | 108 | 34 | 180 | 322 |
| CXL procedures | 233 | 84 | 80 | 397 |

KC – keratoconus; PK – penetrating keratoplasty; DALK – deep anterior lamellar keratoplasty.

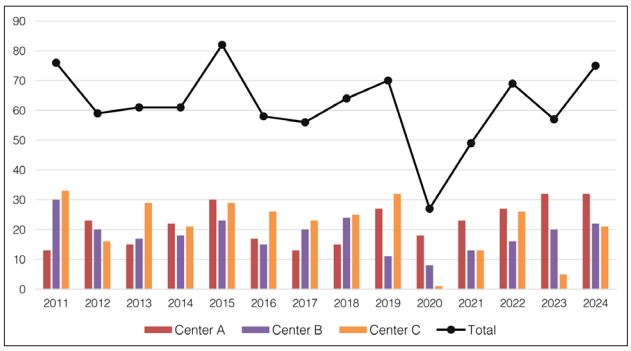



Figure 1. Annual number of transplants performed for keratoconus (KC) at each center between 2011 and 2024. Bars represent the number of KC transplants per year in Centers A–C, while the black line indicates the total number of KC transplants across all centers.

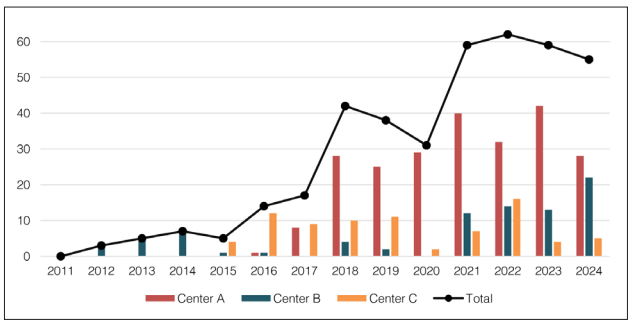



Figure 2. Annual number of corneal collagen cross-linking (CXL) procedures performed at each center between 2011 and 2024. Bars represent the number of procedures per year in Centers A–C, while the black line indicates the total number of CXL procedures across all centers.

CXL procedures were reported in 2012, although only a small number of treatments were performed until 2017. A comparison between 2011-2017 and 2018-2024 periods revealed a significant increase in the annual number of CXL procedures after 2018 (7.3 ± 6.1 to 49.4 ± 12.2, $p<0.001$), representing a rise from 0.70 to 4.71 procedures per million inhabitants (pmi). The mean annual number of transplants for KC decreased from 64.7 ± 10.1 to 58.7 ± 16.5 (6.21 to 5.60 pmi), when comparing the pre- (2011-2017) and the post- (2018-2024) CXL periods, although this difference was not statistically significant ($p=0.427$). The mean age of KC patients undergoing keratoplasty did not differ significantly between the two periods (35.5 ± 2.4 *vs* 34.8 ± 2.0 years,

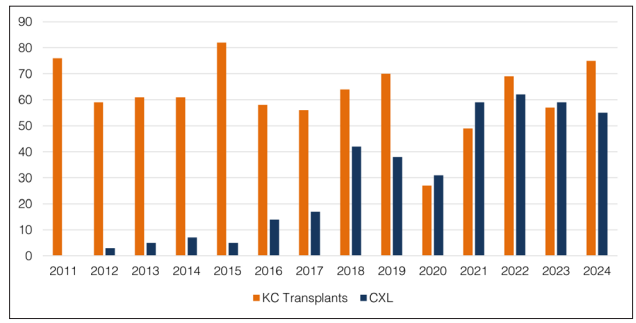



Figure 3. Annual number of keratoconus-related corneal transplants (KC Transplants) and corneal cross-linking (CXL) procedures performed between 2011 and 2024 across all centers.

$p=0.564$). Similar trends were observed when the analysis was performed separately for each center.

An important decline in both corneal transplants and CXL procedures was observed in 2020, coinciding with the COVID-19 pandemic. A one-way ANOVA comparing the pre-pandemic (2017–2019), pandemic (2020), and post-pandemic (2021–2023) periods showed differences in the number of total corneal transplants ($p=0.03$), KC-related transplants ($p=0.05$), and CXL procedures ($p=0.02$).

Linear regression analysis revealed no significant temporal trend in the annual number of transplants performed for KC ($\beta= -0.611$, $p=0.516$). No significant associations were found between the number of CXL procedures and the number of transplants performed for KC in the overall cohort ($\beta =-0.07$, $p=0.64$). Similar results were obtained when each center was analyzed individually. A segmented regression comparing the pre- and post-CXL periods demonstrated a non-significant negative interaction ($\beta= -2.633$, $p=0.389$), suggesting a potential but unconfirmed reduction in transplants for KC with increasing CXL activity in recent years. To explore potential delayed effects of CXL, correlations were tested between transplants for KC and CXL procedures in preceding years. A weak, non-significant negative correlation was found for lag3 ($\varrho= -0.23$; $p=0.50$), corresponding to a three-year delay between CXL procedures and transplant rates. The analysis for a five-year delay also showed no significant correlation.

The ratio between CXL procedures and KC-related transplants increased significantly over time ($\beta= 0.09$, $p<0.001$), reflecting a progressive rise in the relative use of

CXL compared with keratoplasty. Fig. 3 shows the annual trend in the number of CXL procedures compared with corneal transplants for KC.

## DISCUSSION

This is the first study to report national multicenter data on corneal transplants and CXL for keratoconus in Portugal, based on data from three national referral centers for corneal transplantation. A marked rise in CXL procedures was observed since 2018, while the number of keratoplasties for KC remained relatively stable. Despite the growing adoption of CXL, the expected reduction in corneal transplant rates was not significant, even if a negative trend was observed.

Keratoconus remains a relevant indication for corneal transplantation in Portugal, accounting for approximately 15% of all keratoplasties in our cohort, slightly higher than the 12% reported in European studies.[11] This may reflect both the persistence of advanced cases and the referral patterns of the tertiary centers included, which often manage the most severe forms of the disease.

CXL is now globally recognized as the first-line treatment for progressive KC, with proven efficacy in halting disease progression and, in many cases, improving both visual acuity and topographic parameters.[12–14] Following its introduction, several authors hypothesized that the widespread adoption of CXL would lead to a reduction in the need for keratoplasty in keratoconus patients.[4,5,7]

While significant differences were found in the total number of corneal transplants between centers, the number of keratoplasties performed specifically for KC was similar, suggesting comparable patient populations across these tertiary referral centers. In contrast, the marked variation in CXL volume underscores the uneven adoption and dissemination of CXL across the country, despite its global recognition as the standard of care for progressive KC.[5–7] This likely reflects the absence of standardized national guidelines for KC management, leading to variability in clinical decision-making influenced by local expertise, referral patterns, and institutional resources.

Although the annual number of KC-related transplants decreased slightly between the pre- and post-CXL periods, this change was not statistically significant. These findings contrast with those from the Netherlands and Norway, which reported reductions of approximately 25% and over 50%, respectively, in KC-related corneal transplants following CXL implementation.[8,9] In Canada, Sklar *et al* observed a lower proportion of keratoplasties performed for KC after CXL introduction, although the absolute number remained stable.[10] A key metric in this comparison is the ratio of CXL procedures to keratoplasties. In our cohort, the average annual ratio during the post-CXL period was 0.8:1 (49.4 CXL *vs* 58.7 transplants), whereas Godefrooij et al reported a much higher ratio in the Netherlands, with a significant decline in keratoplasty rates occurring precisely as this ratio exceeded a 2:1 threshold.[9] This indicates that CXL adoption in Portugal has yet to reach the critical mass necessary to significantly offset the surgical burden of advanced disease. Taken together, these comparisons suggest that while CXL availability may influence keratoplasty demand, the magnitude and timing of its impact are highly dependent on national implementation strategies and patient demographics.

Several factors may explain the absence of a significant decline in transplants in our series. First, CXL was implemented later and adopted more gradually in Portugal compared with other countries, with a marked expansion only after 2018. Second, the lack of an age limit in our analysis likely contributed to the inclusion of older patients. Patients undergoing CXL were significantly younger than those requiring keratoplasty, many of whom were probably diagnosed before the introduction of CXL and thus represent cases where CXL was no longer indicated. In contrast, Godefrooij *et al* restricted their analysis to patients under 50 years of age, likely capturing a younger, CXL-eligible population with greater preventive potential.[9] Furthermore, the three participating centers serve as referral institutions 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 that attenuates the observed impact of CXL on transplant rates, as these patients often present with more advanced KC for which keratoplasty remains the only viable treatment option.

The steady rise in the ratio between CXL and keratoplasty procedures observed in our study highlights a clear shift toward preventive management over the last decade. Similar to previous reports, this may represent an early phase in the epidemiological transition driven by CXL, where the effect on transplant rates becomes evident only after several years of widespread access. A transient decline in both CXL and transplantation activity was observed in 2020, coinciding with the COVID-19 pandemic, consistent with global reports of surgical volume reductions during this period.[15–17]

Although the overall number of keratoplasties did not show a statistically significant decline, the individual efficacy of CXL in preventing disease progression is well supported by both previous evidence and our results.[12–14] A randomized controlled trial by Wittig-Silva et al demonstrated that within three years, none of the eyes treated with CXL required corneal transplantation, whereas 10% of the untreated eyes needed keratoplasty.[18] In our cohort, only one of the 397 patients who underwent CXL subsequently required a corneal transplant, further reinforcing the role of CXL in modifying the natural history of KC.

Another important consideration is how these findings integrate with global epidemiological trends. Multiple recent studies have reported a substantial rise in both the incidence and prevalence of keratoconus worldwide. A recent population-based study in Germany, for instance, estimated a prevalence ten times higher than previously reported.[19] Although no equivalent national data currently exists for Portugal, there is no reason to believe this rising trend does not apply locally — especially given improvements in diagnostic imaging and growing awareness among clinicians. Furthermore, migratory phenomena to-

ward Europe, alongside possible environmental or genetic contributors, may also play a role in these evolving epidemiological patterns.

Our study has some limitations. Data were collected retrospectively from institutional registries and may be subject to reporting inconsistencies. Marked differences in CXL volume across centers indicate variability in clinical practices, and other concurrent factors or treatments may have influenced keratoplasty trends. Differences in patient demographics, including the referral of advanced cases from abroad, may also have contributed to variability in outcomes. Due to the retrospective nature of the study and the lack of digitized records for earlier periods across centers, individualized clinical and keratometric data were not available for a significant portion of the cohort. Consequently, we were unable to correlate surgical trends with keratoconus staging, which would have allowed for a more robust analysis. Additionally, the absence of detailed clinical and tomographic data precluded a precise characterization of disease severity and surgical indications, and potential changes in thresholds for CXL and keratoplasty over time may have influenced the observed trends. Another limitation of our analysis is the likely underreporting of CXL procedures performed in the private sector, which are not uniformly captured in public health records. While keratoplasty is typically centralized within public tertiary centers and thus reliably documented, CXL is often offered in outpatient private clinics where access may be faster. This discrepancy could contribute to the apparent lack of correlation between increasing CXL numbers and stable transplant rates and underscores the need for more comprehensive registries. Nevertheless, this multicenter study, based on 14 years of data from the three main national referral centers, provides a robust and representative overview of KC-related surgical activity in Portugal.

In conclusion, although the use of CXL has increased substantially in recent years, this wider availability has not yet translated into a measurable reduction in keratoconus-related corneal transplants in our country. Beyond its clinical implications, this study highlights the critical need to transition from isolated procedure counts and fragmented datasets toward a more integrated, population-level understanding of keratoconus care. While the efficacy of corneal cross-linking has been established in multiple high-quality clinical trials, its broader public health impact remains poorly characterized. We need a shift from clinic-focused evidence to system-focused evidence — from proving that a treatment works, to proving that it works at scale, across diverse populations, and within the limitations of real-world health systems. This requires not only longitudinal and multicenter data, but also the same level of methodological rigor, transparency, and accountability that we demand of clinical trials. In an era of rising keratoconus prevalence and expanding therapeutic options, health policy decisions must be grounded in robust, real-world evidence that reflects both clinical outcomes and system-level performance. Within the framework of standardized management guidelines, the clinical significance of CXL necessitates a sustained effort to minimize treatment latency and reduce waiting lists, thereby preventing progression to advanced stages. Only by bridging the gap between efficacy and implementation can we optimize care delivery and ensure equitable, early access to vision-preserving interventions like CXL.

## CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

MF: Conceptualization, data collection, formal analysis, writing original draft.

PG, JG: Conceptualization, data collection, formal analysis, writing - review & editing.

RG, JPS, MMN, LO: Data collection, formal analysis, writing - review & editing.

NA, VM, JF, EC, AR, CT, MJQ: Writing - review & editing.

All authors approved the final version of the manuscript for publication and assume responsibility for all aspects of the work, ensuring the accuracy and integrity of the data presented.

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

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

RG, JPS, MMN, LO: Recolha de dados, análise formal, redação – revisão e edição.

NA, VM, JF, EC, AR, CT, MJQ: redação – revisão e edição.

Todos os autores aprovaram a versão final do manuscrito para publicação e assumem responsabilidade por todos os aspetos do trabalho, garantindo a exatidão e a integridade dos dados apresentados.

## RESPONSABILIDADES ÉTICAS

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

**Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo.

**Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

**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.

## ETHICAL DISCLOSURES

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Protection of Human and Animal Subjects:** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

**Provenance and Peer Review:** Not commissioned; externally peer-reviewed.

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