Visual Outcomes in Children with Craniosynostosis: Experience from a National Tertiary Referral Center

Prognóstico Visual em Crianças com Craniossinostoses: Experiência de um Centro de Referência Nacional

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ABSTRACT

INTRODUCTION: Craniosynostosis is a rare craniofacial disorder frequently associated with ophthalmologic morbidity. The impact of cranial surgery timing on visual outcomes remains controversial. This study evaluated ophthalmologic outcomes in children with craniosynostosis treated at a national tertiary referral center in Portugal, focusing on the influence of surgical timing and syndromic status on visual function.

METHODS: A retrospective study included all children with genetically or clinically confirmed craniosynostosis assessed by ophthalmology and neurosurgery departments between January 2014 and August 2025. Demographic, genetic, surgical and ophthalmic data were collected. Patients were categorized by surgical timing: early (≤ 6 months) or late surgery (> 6 months). Logistic regression models assessed associations between surgical timing, syndromic status and visual outcomes.

RESULTS: Thirty-seven patients were included (76% syndromic). Multiple-suture involvement occurred in 21 (57%), with the coronal suture most frequently affected (41%). Median age at the first neurosurgery was 7.0 months (IQR 4.0-16.5). Genetically confirmed syndromic craniosynostosis was present in 27 patients (73%), most commonly Crouzon (n=9), Muenke (n=5), Apert (n=4) and Pfeiffer (n=3). Nineteen distinct pathogenic variants were identified, predominantly in the *FGFR2 gene* (n=7) and *FGFR3* (n=5), with novel variants in *GLI3* and *EFNB1*.

Late surgery was associated with higher odds of amblyopia (OR=2.75, 95%CI:0.50-14.99, *p*=0.243). Syndromic craniosynostosis independently conferred a ten-fold increased risk of strabismus (OR=10.23, 95%CI: 1.61–64.8, *p*=0.014) and a greater risk of amblyopia (OR=3.46, 95% CI: 0.35–34.42, *p*=0.289). Multiple-suture involvement displayed a trend toward optic atrophy (OR=3.57, *p*=0.23). At baseline, 38.5% had amblyopia, 66.7% strabismus and 81.1% papilledema. At final follow-up (mean 6.5 years), amblyopia persisted in 28.6%, strabismus in 78.4%, and optic atrophy developed in 21.6%; papilledema resolved in all.

CONCLUSION: This first Portuguese cohort integrating clinical, surgical and genetic data underscores the significant visual morbidity of craniosynostosis. Syndromic status emerged as the main determinant of adverse ophthalmologic outcomes, while earlier cranial surgery showed a potentially protective effect on visual development. The identification of novel pathogenic vari-

ants expands the molecular spectrum of craniosynostosis. Early referral, comprehensive genetic evaluation and long-term ophthalmologic surveillance remain crucial to preserve vision in this vulnerable population.

KEYWORDS: Child; Craniosynostoses/complications; Craniosynostoses/surgery; Vision Disorders/etiology Visual Acuity.

RESUMO

INTRODUÇÃO: As craniossinostoses são dismorfias craniofaciais raras, frequentemente associadas a significativa morbilidade oftalmológica. O impacto do momento da cirurgia craniana no prognóstico visual permanece controverso. Este estudo avaliou o desenvolvimento visual em crianças com craniossinostoses num centro de referência, com ênfase na influência do momento cirúrgico e do carácter sindrómico sobre a função visual.

MÉTODOS: Estudo retrospetivo incluindo todas as crianças com diagnóstico clínico ou genético confirmado de craniossinostoses, avaliadas por Oftalmologia e Neurocirurgia entre janeiro de 2014 e agosto de 2025. Dados demográficos, genéticos, cirúrgicos e oftalmológicos foram recolhidos. Os doentes foram classificados segundo o momento cirúrgico: precoce (≤6 meses de idade) ou tardio (>6 meses). Modelos de regressão logística avaliaram as associações entre o momento da cirurgia, o carácter sindrómico e a função visual.

RESULTADOS: Foram incluídos 37 doentes (76% sindrómicos). O envolvimento de múltiplas suturas verificou-se em 21 (57%), sendo a coronal a mais frequentemente afetada (41%). A mediana da idade na primeira cirurgia foi de 7,0 meses (IQR 4,0–16,5). Craniossinostoses sindrómicas foram geneticamente confirmadas em 27 doentes (73%), mais frequentemente Crouzon (n=9), Muenke (n=5), Apert (n=4) e Pfeiffer (n=3). Identificaram-se 19 variantes patogénicas distintas, predominantemente nos genes *FGFR2* (n=7) e *FGFR3* (n=5), incluindo novas variantes nos genes *GLI3* e *EFNB1*.

A cirurgia tardia associou-se a maior probabilidade de ambliopia (OR=2,75; IC95%:0,50–14,99; *p*=0,243). A forma sindrómica conferiu um risco superior de estrabismo (OR=10,23; IC95%:1,61–64,8; *p*=0,014) e de ambliopia (OR=3,46;IC95%:0,35–34,42; *p*=0,289). O envolvimento de múltiplas suturas demonstrou tendência para atrofia ótica (OR=3,57; *p*=0,23). Na avaliação inicial, 38,5% apresentavam ambliopia, 66,7% estrabismo e 81,1% papiledema. Na avaliação final, a ambliopia persistia em 28,6%, estrabismo em 78,4% e atrofia ótica em 21,6%; o papiledema resolveu em todos os casos.

CONCLUSÃO: Esta é a primeira coorte portuguesa a integrar dados clínicos, cirúrgicos e genéticos e que enfatizou a elevada morbilidade nas craniossinostoses. O carácter sindrómico revelou-se o principal determinante de pior prognóstico visual, enquanto a cirurgia precoce evidenciou um possível efeito protetor no desenvolvimento visual. A identificação de novas variantes genéticas alargou o espetro molecular da doença. A referenciação atempada, a avaliação genética abrangente e uma vigilância oftalmológica prolongada são cruciais para preservar a visão nesta população vulnerável.

PALAVRAS-CHAVE: Acuidade Visual; Craniossinostoses/cirurgia; Craniossinostoses/complicações; Criança; Perturbações da Visão.

INTRODUCTION

Craniosynostosis is characterized by the premature fusion of one or more cranial sutures, resulting in craniofacial skeletal development abnormalities, neurocognitive impairment and substantial visual morbidity.[1–3] Although still classified as a rare disease, with estimated prevalence ranging from 1 in 1400 to 1 in 2500 live births worldwide[2–5] with a recent increase in estimated prevalence,[6] its substantial infant morbidity and public health burden[7] warrant a specialized multidisciplinary management. Primary craniosynostosis can be classified as nonsyndromic, accounting for 70%-85% of cases, or syndromic, encompassing over 180 distinct entities such as Apert, Crouzon, Pfeiffer and Saethre-Chotzen syndromes.[1,4,8] Syndromic forms are often derived from gain-of-function pathogenic variants in the fibroblast growth factor receptor (*FGFR*) genes or related genes such as *TWIST*[1,8] and typically present with more complex craniofacial anomalies and severe ophthalmologic involvement. Patients with craniosynostosis should be referred for genetic evaluation, particularly if multiple suture involvement, ad-

ditional abnormalities or positive family history.

Visual morbidity is common among these patients, with 65% of syndromic cases having a visual acuity less than 6/12 in at least one eye and 40% in both eyes.[9] Several mechanisms have been proposed for visual impairment, including raised intracranial pressure, optic neuropathy and amblyopia secondary to corneal scarring, strabismus or refractive errors. Other ocular manifestations include proptosis, enophthalmos, eyelid ptosis and optic nerve hypoplasia.[1,8] Prompt recognition and timely management are critical to prevent irreversible vision loss, as a fully developed and mature visual system is attained at 10 years of age, with amblyopia treatment results being overall unsuccessful after the age of eight years.[1]

The timing of cranial vault expansion remains a critical yet controversial issue. While early intervention is hypothesized to mitigate visual morbidity by relieving intracranial pressure and allowing adequate visual development,[10–13] evidence remains controversial. Recent reports indicate no clear causal relationship between cranial surgical timing and ophthalmologic outcomes.[14] To date, no Portuguese cohort has systematically investigated ophthalmologic outcomes in craniosynostosis, and few studies worldwide have evaluated the impact of surgical timing while accounting for syndromic status.

This study aimed to evaluate ophthalmologic outcomes in children with craniosynostosis treated at a national tertiary referral centre in Portugal, with a particular focus on the impact of cranial surgery timing (≤6 *vs* >6 months) and syndromic status. By combining clinical, surgical, and genetic perspectives, we sought to evaluate determinants of visual prognosis in this rare but high-risk population.

MATERIAL AND METHODS

STUDY DESIGN, SETTING AND PARTICIPANTS

A retrospective observational cohort study was conducted at a national tertiary referral center in Portugal. Eligible participants were children (0-18 years old) with a confirmed diagnosis of craniosynostosis who were jointly evaluated by the neurosurgery and ophthalmology departments between January 2014 and August 2025. Exclusion criteria included alternative diagnoses, absence of cranial surgery and loss to follow-up. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethical review committee (90/26). Written informed consent was obtained from all legal guardians prior to surgical intervention and genetic testing.

DATA COLLECTION

Demographic and clinical data were extracted from institutional electronic medical records. Genetic data were obtained retrospectively from the same records. Genetic findings were interpreted in accordance with the American College of Medical Genetics and Genomics (ACMG) standards and guidelines, and variant classifications were cross-referenced using the ClinVar platform (National Center for Biotechnology Information, 2025).[15] Patients were classified as syndromic or non-syndromic based on integrated clinical assessment and molecular diagnosis.

OPHTHALMOLOGIC OUTCOMES

Best-corrected visual acuity (BCVA) was quantified using standardized age-appropriate protocols and classified according to American Academy of Ophthalmology (AAO) criteria for amblyopia.[16] Cycloplegic refraction was performed with age-appropriate agents, and astigmatism orientation was defined using Denis *et al* criteria[10] (with-the-rule (WTR): 175°–5°; against-the-rule (ATR): 85°–95°). Ocular alignment and motility were systematically evaluated. Optic nerve pathology, including papilledema and atrophy, was assessed by ophthalmoscopy and optical coherence tomography (OCT) when available. Corneal involvement, including corneal scarring and exposure keratitis, was additionally recorded.

SURGICAL TIMING

Surgical timing was defined by age at first cranial surgery as: early surgery (≤6 months) or late surgery (>6 months).

OUTCOMES

The primary outcome was the association between cranial surgical timing (early *vs* late) and final visual outcomes (amblyopia, strabismus, papilledema, optic atrophy). Secondary outcomes included the description of baseline ophthalmologic findings, comparison of visual outcomes between syndromic and non-syndromic patients, impact of isolated versus multiple suture involvement, and integration of genetic data, including novel variants detected in our population.

STATISTICAL ANALYSIS

Continuous variables were compared using the Mann–Whitney U test; categorical variables with Fisher's exact test or the Fisher–Freeman–Halton test, as appropriate. Normality was tested according to Kolmogorov-Smirnov or skewness and kurtosis. For binary outcomes, McNemar's test was used to evaluate agreement between baseline and last follow-up evaluations. Logistic regression models were used to estimate crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) for associations between surgical timing and visual prognosis. Adjustment was performed for syndromic status and suture involvement. Kaplan-Meier curves were generated to compare time to first cranial surgery by syndromic status, with differences assessed using the log-rank test. Denominators reported available data per variable; no data imputation was performed. A p-value of <0.05 was regarded as statistically significant. Statistical analysis was performed using R Statistical Software (version 4.4.2; R Core Team 2024).

RESULTS

PARTICIPANTS

A total of 63 patients with craniosynostosis were evaluated during the study period, of whom 26 were excluded from the cohort due to loss to follow-up. A total of 37 were

included in the final analysis (Fig. 1). Of these, 28 (75.7%) had syndromic craniosynostosis and 9 (24.3%) had non-syndromic forms. The median age at first cranial surgery was 7.0 months (IQR 4.0-16.5). The most common first neurosurgery performed was cranial vault distractors. Twenty-eight children (75.7%) required at least two cranial surgeries during follow-up. Multiple sutures were involved in 21 patients (56.8%), with the coronal suture most frequently affected (n=15, 40.5%). Bilateral involvement was more common in syndromic patients (92.9% *vs* 66.7%, *p*=0.081). Baseline characteristics of the study cohort are summarized in Table 1. Mean age at first ophthalmologic evaluation was 68.97±56.26 months and at last evaluation was 12.6±5.9 years; mean follow-up time was 6.48±4.36 years.

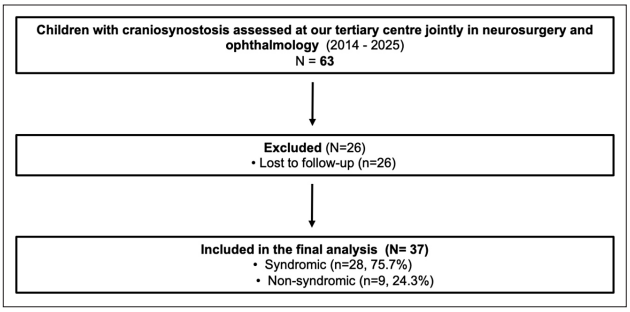


Figure 1. Flow diagram of the study population

GENETIC DIAGNOSIS

Genetic testing was performed in 34 of the 37 patients (91.9%). Detailed phenotypic and genotypic findings available are presented in Table 2. Genetically confirmed syndromic craniosynostosis was identified in 28 patients (76%), including Crouzon (n = 9), Muenke (n = 5), Apert (n = 4), Pfeiffer (n = 3), Saethre Chotzen (n = 2), Greig (n = 2), craniofacial dysplasia with X linked inheritance (n = 1), and Turner like intellectual developmental syndrome (n = 1).

A pathogenic *FGFR2* variant (c.1025G>T) was detected in one patient with a phenotype broadly consistent with Jackson–Weiss syndrome, although presenting atypical features, including broad thumbs.

In total, 13 distinct variants were identified in 6 different genes (*FGFR2*, *FGFR3*, *TWIST1*, *HUWE1*, *GLI3*, *EFNB1*). The most frequently identified variant was c. 749C>G (p.Pro250Arg) in gene FGFR3 (n = 4). Based on ACMG criteria, 13 variants were classified as pathogenic, 2 as likely pathogenic, and 1 as of uncertain significance. A high proportion of the variants identified in this cohort were missense changes (n=15), reflecting the predominance of single amino acid substitutions contributing to craniosynostosis pathogenesis.[17] Two variants - c.1835C>A in *GLI3*, and c.406+2_406+3del in *EFNB1* - have not been previously reported and may represent novel changes.

PRIMARY OUTCOME

Patients undergoing surgery after 6 months of age showed 2.7-fold higher odds of amblyopia compared with early surgery, although results did not reach statistical significance (OR = 2.75, 95%CI: 0.50–14.99, p=0.243) (Table 3, Fig. 2). Syndromic craniosynostosis was also associated with an increased risk of amblyopia (OR=3.46, 95%CI: 0.35–34.42, *p*=0.289).

Late surgery was not significantly associated with strabismus (OR=2.43, 95%CI: 0.30–19.6, *p*=0.405). However, syndromic craniosynostosis conferred a significantly increased risk of strabismus independent of surgical timing (OR=10.23, 95%CI: 1.61–64.8, *p*=0.014). A trend towards higher odds of optic atrophy was observed for patients with multiple-suture involvement (OR=3.57, 95%CI: 0.44–28.9, *p*=0.234).

In adjusted models, neither timing of surgery (OR=1.50; 95%CI 0.26–8.70; *p*=0.650) nor syndromic status (OR=2.11, 95%CI: 0.20–22.2, *p*=0.534) increased the odds of optic atrophy.

Although papilledema was diagnosed in several patients at initial diagnosis (30/37 patients; 81.1%), no patient presented at the final evaluation.

Table 1. Baseline characteristics of the study population.

Characteristic	Total (N= 37)	Non-syndromic (N= 9)	Syndromic (N= 28)	*p*-value
Age at surgery (months), median (P25-P75)	7.0 (4.0-16.5)	7.00 (5.0-24.0)	8.00 (4.0-17.3)	0.901
Female gender, n (%)	23 (62.2)	5 (55.6)	18 (64.3)	0.705
Number of sutures involved, n (%)				
Simple	16 (43.2)	5 (55.6)	11 (39.3)	0.458
Multiple	21 (56.8)	4 (44.4)	17 (60.7)	
Type of suture involved, n (%)				
Coronal	15 (40.5)	4 (44.4)	11 (39.3)	0.258
Sagittal	1 (2.7)	1 (11.1)	0 (0)	
Multiple	21 (56.8)	5 (44.4)	17 (60.7)	
Laterality, n (%)				
Unilateral	5 (13.5)	3 (33.3)	2 (7.1)	0.081
Bilateral	32 (86.5)	6 (66.7)	26 (92.9)	

Cohort characteristics are presented for the total population (N=37), non-syndromic (n=9), and syndromic patients (n=28). Continuous variables are expressed as median (interquartile range, P25-P75); categorical variables as number (percentage). Comparisons between groups were made using the Mann–Whitney U test for continuous variables and Fisher's exact test (or Fisher–Freeman–Halton exact test if >2 categories) for categorical variables.

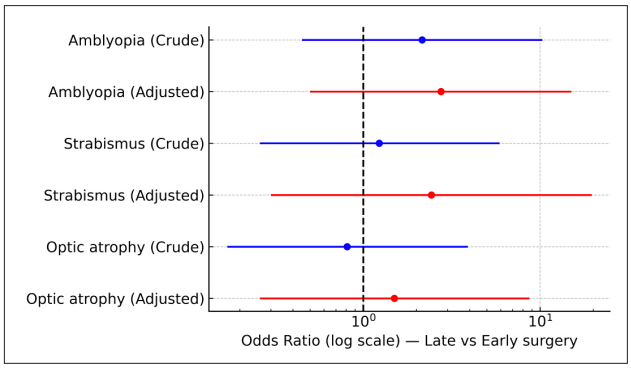


Figure 2. Forest plot of crude and adjusted odds ratios (OR) for visual outcomes comparing late (>6 months) versus early (≤6 months) surgery.

OR are shown on a log scale with 95% confidence intervals. Adjusted models account for syndromic status and suture class. Dotted vertical line represents OR = 1.

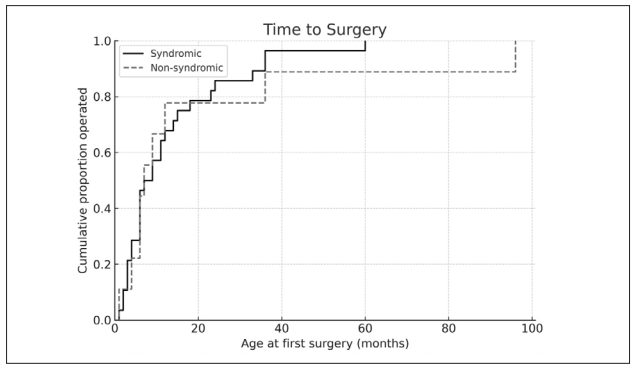


Figure 3. Kaplan–Meier curves of age at first cranial surgery stratified by syndromic status.

Cumulative proportion of patients undergoing surgery is plotted against age (in months). Solid line represents syndromic craniosynostosis and dashed line represents non-syndromic cases.

Table 2. Genetic variants identified in the study population

Pt	Gene	Transcript (NM_)	Location	Molecular consequence	Variant (HGVS c./p.)	ACMG Class	Phenotype (syndrome)
1	FGFR3	NM_000142.5	4p16.3	Missense	c.749C>G (p.Pro250Arg)	Pathogenic	Muenke
2	TWIST1	NM_000474.4	7p21.1	Inframe insertion	c.397_417dup (p.Lys133_Pro139dup)	Pathogenic	Saethre-Chotzen
3	EFNB1	**Novel**	Xq13.1		c.406+2_406+3del(p-?) in intron 2		Craniofacial dysplasia with X-linked inheritance
4	FGFR3	NM_000142.5	4p16.3	Missense	c.749C>G (p.Pro250Arg)	Pathogenic	Muenke
5	HUWE1	NM_031407.7	Xp11.22	Missense	c.329G>A (p. Arg110Gln)	Pathogenic	Turner-like intellectual developmental syndrome
6	FGFR2	NM_000141.5	10q26.13	Missense	c.1977G>C (p.Lys659Asn)	Pathogenic	Crouzon
7	FGFR2	NM_000141.5	10q26.13	Missense	c.868T>C (p.Trp290Arg)	Pathogenic	Crouzon
8	GLI3	**Novel**			c.1835C>A (p.Pro612Gln)		Greig
9	FGFR2	NM_000141.5	10q26.13	Missense	c.1052C>G (p.Ser351Cys)	Pathogenic	Pfeiffer
10	FGFR2	NM_000141.5	10q26.13	Missense	c.1025G>C (p.Cys342Ser)	Pathogenic	Crouzon
11	FGFR2	NM_000141.5	10q26.13	Missense	c.755C>G (p.Ser252Trp)	Pathogenic	Apert
12	FGFR2	NM_000141.5	10q26.14	Missense	c.1025G>T (p.Cys342Phe)	Pathogenic	Crouzon
13	FGFR3	NM_000142.5	4p16.3	Missense	c.749C>G (p.Pro250Arg)	Pathogenic	Muenke
14	TWIST1	NM_000474.4	7p21.1	Missense	c.445C>T (p.Leu149Phe)	Likely Pathogenic	Saethre-Chotzen
15	FGFR3	NM_000142.5	4p16.3	Missense	c.749C>G (p.Pro250Arg)	Pathogenic	Muenke
16	GLI3	NM_000168.6	7p14.1	Missense	c.2587C>T (p.Arg863Cys)	VUS	Greig
17	FGFR3	NM_000142.5	4p16.3	Missense	c.749C>G (p.Pro250Arg)	Pathogenic	Muenke

Listed are the causative variants per patient, with ACMG classification when available. Variants labeled "Novel" had not been previously reported in ClinVar at the time of analysis. Most relevant phenotype features are summarized.

ACMG- American College of Medical Genetics and Genomics; Pt- Patient; VUS- variant of uncertain significance.

OPHTALMOLOGIC OUTCOMES

Baseline evaluation

At the first ophthalmic evaluation, amblyopia was present in 38.5% (10/26), and it was more frequent in syndromic cases compared with non-syndromic cases (45.0% *vs* 16.7%, *p*=0.352) (Table 1.A.). A total of 66.7% presented strabismus at initial assessment (32% exotropia, 16% esotropia), while papilledema was noted in 81.1%. Stratified by syndromic status, strabismus was present in 74.1% of syndromic patients (20/27) and in 44.4% of non-syndromic patients (4/9) (*p*=0.126). No optic atrophy was observed initially. Median spherical equivalent (SE) (in diopters) at baseline in the best eye was +0.01 (0.00-1.63) and +0.35 (-0.19–1.9) in the worst

Table 3. Visual outcomes according to timing of surgery (late >6 *vs* early ≤6 months).

Outcome	Early surgery, n (%)	Late surgery, n (%)	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Amblyopia	3/15 (20.0)	7/20 (35.0)	2.15 (0.45–10.29)	0.458	2.75 (0.50–14.99)	0.243
Optic atrophy	4/17 (23.5)	4/20 (20.0)	0.813 (0.169-3.895)	1.00	1.50 (0.26–8.70)	0.650
Strabismus	13/17 (76.5)	16/20 (80.0)	1.231 (0.257-5.900)	1.00	2.43 (0.30–19.6)	0.405
Exotropia	4/36 (11.1)	7/36 (19.4)	-	-	-	-
Esotropia	2/36 (5.6)	1/36 (2.8)	-	-	-	-
Alphabetic pattern	10/17 (58.8)	16/20 (80.0)	-	-	-	-
Corneal complications						
Exposure keratopathy	1/37 (2.7)	3/37 (8.1)	-	-	-	-
Corneal scarring	1/37 (2.7)	1/37 (2.7)	-	-	-	-

Values are presented as n (%) and odds ratios (OR) with 95% confidence intervals. Denominators reflect the number of patients with available data for each outcome. *p*-values were calculated using Fisher's exact test. Adjusted models account for syndromic status and suture class. Subtypes of strabismus and corneal complications are presented descriptively (n/N, %)

eye. Most commonly the patients presented (n=17, 45.9%) astigmatism, mostly oblique astigmatism (13.5% WTR *vs* 8.1% ATR).

Final evaluation

At the final follow-up, amblyopia improved to 28.6% of cases (McNemar *p*=0.625), strabismus persisted in 78.4%, and optic atrophy developed in 21.6%; no patient had papilledema at the last follow-up (Table 3). Amblyopia was secondary to optic atrophy (n=4, 10.8%), strabismus (n=2, 5.4%), anisometropia (n=5, 13.5%) and mixed etiology (n=1, 2.7%). Median SE (in diopters) in the best eye was +0.03 (-0.31–0.57) and +0.35 (-0.2–1.9) in the worst eye. Astigmatism remained the most common refractive error (n=25, 67.6%), being mostly oblique (18.9% WTR *vs* 16.2% ATR). Ptosis was diagnosed in 6 (16.2%) of cases, with 2 cases (5.4%) requiring surgical correction. At last evaluation, eight patients (21.6%) presented lagophthalmos, four (10.8%) exposure keratitis and one (2.7%) corneal scarring involving the visual axis.

Stratified by type of strabismus, alphabetic patterns of strabismus were diagnosed in 70.3% (58.8% early *vs* 80.0% late surgery; *p*=0.160); exotropia was present in 30.6% (11.1% early *vs* 19.4% late surgery; *p*=0.718); and esotropia was present in 8.3% (5.6% early *vs* 2.8% late surgery; *p*=0.574). Strabismus surgery was performed in 6 (16.2%) patients, 100% (n=6) with improvement in angles of deviation. Botulinum toxin was used in 2 (5.4%) patients. One patient (2.7%) was prescribed prisms. Three patients (8.1%) presented nystagmus at last evaluation, while four (10.8%) presented torticollis.

When stratified by timing of surgery, amblyopia was more frequent in those operated after 6 months (35.0% *vs* 20.0%), although not statistically significant (*p*=0.458). Frequencies of strabismus and optic atrophy were elevated in both groups, with no significant differences (Fig. 1.A.).

SURGICAL TIMING

Kaplan–Meier analysis suggested syndromic children undergo surgery earlier, although not reaching a statistically significant result (Fig. 3).

DISCUSSION

To our knowledge, this study represents the first national Portuguese cohort systematically addressing ophthalmologic outcomes in children with craniosynostosis, integrating clinical, surgical and genetic perspectives. Our findings confirm that, despite advances in craniofacial surgery, visual morbidity remains significant: nearly one-third of children developed amblyopia, over three-quarters presented strabismus, and one in five progressed to optic atrophy. These results, consistent with previous reports in the literature,[1,18] support the need for systematic, long-term ophthalmological surveillance as a vital component of craniosynostosis care.

The timing of craniofacial surgery remains controversial as a determinant of visual prognosis. In our cohort, children undergoing surgery after 6 months of age presented more than double the odds of amblyopia compared with earlier surgery, although the effect did not reach statistical significance. Despite the wide confidence intervals reflecting a small sample size, the direction of effect suggests a protective role of earlier intervention on visual development. This is consistent with earlier reports supporting the benefits of early intervention by reducing intracranial pressure, restoring orbital anatomy and preventing amblyogenic mechanisms, including ocular misalignment precluding binocular vision established early in visual development.[3,10–12] These results also support the hypothesis that visual maturation is delayed yet not persistently affected in these patients.[19]

Syndromic status emerged as the strongest determinant of visual outcome. Children with syndromic craniosynostosis carried a ten-fold increased risk of strabismus development, and a greater chance of amblyopia and optic atrophy, independent of surgical timing. These results are consistent with prior studies demonstrating more severe and persistent visual morbidity in syndromic cases, reflecting the greater craniofacial complexity in this subgroup with a greater num-

ber of ocular abnormalities precluding normal visual development.[1] No clear guidelines regarding the age of screening, screening technique and optimal time have been proposed; however, as suggested by our study and others, syndromic cases require more periodic ophthalmological evaluations than some isolated craniosynostosis.[8,20]

Suture involvement may further impact visual prognosis. Whilst the number of affected sutures did not correlate with amblyopia, multiple-suture involvement showed a strong tendency toward optic atrophy. Albeit not statistically significant, the magnitude of this association suggests a clinically significant association that warrants a rigorous ophthalmic surveillance of children with complex synostosis.

Strabismus is reported in 29% to 90% of cases, mostly attributed to the change of orbital musculature derived from the change in the orbital anatomy resulting in its exocyclorotation.[1,18] Alphabetic patterns were the most common type of strabismus in our cohort. The V-pattern in these children is thought to be caused by the extorsion of the rectus muscle pulleys.[1] Cranial vault expansion changes muscular function with both consecutive improvement and worsening of strabismus.[18,21] In our cohort, no increase in strabismus was denoted following craniofacial surgery.

Limitations of the study included those inherent to its retrospective design and modest sample size, constraining statistical power and precision. Moreover, nearly one-quarter of initially eligible patients were lost to follow-up, a challenge encountered in a tertiary referral centre caring for children from remote areas. Nevertheless, its strengths lie in the integration of clinical, surgical, and genetic data, and the identification of novel genetic variants, providing a comprehensive national perspective on this rare but high-risk condition.

CONCLUSION

In summary, this first Portuguese craniosynostosis cohort highlights the notable burden of visual morbidity in craniosynostosis, with syndromic status emerging as the strongest determinant of adverse visual outcomes. Although not conclusive, trends observed for surgical timing and suture complexity suggest potential paths to improve prognosis. These findings underline the major need for early referral, genetic evaluation, and comprehensive ophthalmologic surveillance. Future multicenter, prospective studies are warranted to define causal relationships and optimize management strategies for this vulnerable population.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

JP: Conceptualization, data collection, data analysis, manuscript drafting.

RR e FT: Conceptualization and critical revision.

BD, SD, ACF, SL, MMS, JM, IL, GF, CF: Critical revision.

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.

JP: Conceptualização, recolha e análise de dados, escrita do manuscrito.

RR, FT: Conceptualização, recolha de dados e revisão crítica.

BD, SD, ACF, SL, MMS, JM, IL, GF, CF: Revisão crítica do manuscrito.

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.

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SUPPLEMENTARY

Table 1.A. Baseline visual outcomes at presentation.

Visual parameter	Total (N=37)	Syndromic (N=28)	Non-syndromic (N= 9)	*p*-value
Amblyopia, n/N (%)	10/26 (38.5)	9/20 (45.0)	1/6 (16.7)	0.352
Strabismus, n/N (%)	24/36 (66.7)	20/27 (74.1)	4/9 (44.4)	0.126
Papilledema, n/N (%)	30/37 (81.1)	21/28 (75.0)	9/9 (100)	0.160
Optic atrophy, n/N (%)	0 (0)	0(0)	0(0)	N.A.

Baseline ophthalmologic findings in children with craniosynostosis at initial presentation, stratified by syndromic *versus* non-syndromic cases. Values are given as n/N (%) with denominators reflecting available data for each parameter. Fisher's exact test was used for categorical comparisons; N.A. (not applicable) applied if no cases were observed.

Table 2.A. Logistic regression models for visual outcomes by syndromic status.

Outcome	Non-syndromic OR (95% CI)	*p*-value	Syndromic OR (95%CI	*p*-value
Amblyopia	Not estimable (0 cases)	1.00	2.0 (0.38–10.6)	0.68
Strabismus	3.0 (0.2–46.6)	0.52	0.57 (0.05–6.3)	1.00
Papilledema	Not estimable (0 cases)	—	0.25 (0.04–1.5)	0.20
Optic atrophy	Not estimable (0 cases)	1.00	0.57 (0.11–2.94)	0.67

Odds ratios (OR) with 95% confidence intervals are shown. Logistic regression was not estimable when no cases were present in a given group; in such cases, Fisher's exact test was applied. No cases of papilledema occurred in non-syndromic patients, so analysis was not possible.

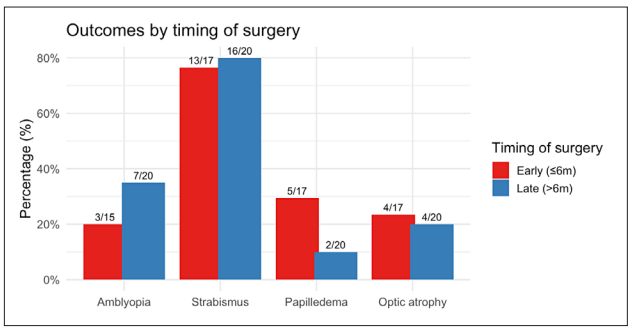


Figure 1.A. Ophthalmological outcomes according to timing of surgery (early ≤6 months *vs* late >6 months).

Bar chart shows the proportion of patients developing amblyopia, strabismus, papilledema (at any point during the disease course), or optic atrophy. Values above bars represent the number of affected patients/total data available.