Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Phenylalanine-associated ocular risk stratification in early-treated children with phenylketonuria: a cross-sectional study

Heba ElTaher
Mansoura University
Dina Laimon
Mansoura University
Mohamed Abdelghafar Hussein
Mohammed_abdelghafar@med.kfs.edu.eg
Kafrelsheikh University

Research Article

Keywords: Phenylketonuria, Ocular findings, Diet regiment

Posted Date: March 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8929509/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose

Although phenylketonuria (PKU) is primarily recognized for its neurological sequelae, the extent and metabolic correlates of ocular involvement in early-treated pediatric patients remain insufficiently characterized. This study aimed to evaluate ocular findings in children with PKU and to examine their association with serum phenylalanine levels, with particular focus on quantitative risk stratification.

Methods

This cross-sectional study included 33 children less than 18 years diagnosed with phenylketonuria (PKU) by neonatal or selective screening and receiving regular follow-up at the Metabolic unit of Mansoura University Children's Hospital, after obtaining informed parental consent. All participants underwent a comprehensive ophthalmological evaluation, including visual acuity assessment, cycloplegic refraction, anterior segment examination, fundus evaluation, intraocular pressure measurement, and ocular motility assessment. Serum phenylalanine levels were recorded, and receiver operating characteristic (ROC) curve analyses were performed to explore phenylalanine thresholds associated with ocular abnormalities.

Results

Ocular abnormalities were observed in a substantial proportion of participants and involved both anterior and posterior segments. Higher serum phenylalanine levels were significantly associated with increased likelihood of ocular involvement. ROC analysis identified phenylalanine ranges associated with elevated ocular risk, providing a quantitative framework for metabolic risk stratification..

Conclusion

Ocular abnormalities may occur in early-treated children with PKU and appear to be associated with phenylalanine control. Quantitative phenylalanine thresholds identified through ROC analysis may support risk-stratified ophthalmic surveillance strategies in pediatric PKU.

What is already known

PKU primarily affects the central nervous system, and elevated phenylalanine levels have been associated with visual dysfunction and occasional ocular abnormalities such as hypopigmentation, refractive errors, and cataract, mostly reported as isolated findings.

What is new

Ocular abnormalities are common and multisystemic in children with PKU and show a clear dose–response relationship with serum phenylalanine levels; this study defines phenylalanine cutoff values (>500 and >1000 μmol/L) associated with increased ocular risk, supporting the eye as a sensitive metabolic target and a potential tool for phenylalanine-guided ophthalmic screening.

Introduction

Phenylketonuria (PKU) is an inherited metabolic disorder caused by deficiency of the enzyme phenylalanine hydroxylase, resulting in elevated blood phenylalanine (Phe) concentrations. Before the introduction of neonatal screening programs in the 1960s, untreated PKU commonly led to severe intellectual disability, emotional and psychosocial disturbances, and irreversible neurological damage(1). Since the implementation of national neonatal PKU screening programs, early diagnosis and dietary intervention have markedly improved neurological outcomes. In Egypt, a national neonatal PKU screening initiative was established in collaboration with the Ministry of Health in 2015, enabling early identification of affected infants and initiation of a Phe-restricted diet, which effectively lowers blood phenylalanine levels and prevents severe intellectual disability(2). Current recommendations emphasize lifelong adherence to dietary treatment in individuals with PKU. However, maintaining strict dietary control becomes increasingly challenging during late childhood and adolescence, when social factors and dietary independence often result in suboptimal metabolic control(3). Regular monitoring of blood phenylalanine concentrations remains the cornerstone of treatment follow-up, and specific target ranges have been recommended for special populations, including women planning pregnancy and during gestation (120–360 μmol/L) (4).

PKU is conventionally classified according to pretreatment blood phenylalanine concentrations and dietary phenylalanine tolerance, ranging from classical PKU (cPKU), with pretreatment Phe levels exceeding 1200 μmol/L, to mild PKU (mPKU; 600–1200 μmol/L) and mild hyperphenylalaninemia (MHP; 120–600 μmol/L) (5). At elevated concentrations, phenylalanine competes with other large neutral amino acids for transport across the blood–brain barrier and into peripheral tissues, leading to amino acid imbalances that contribute to impaired myelination and oligodendrocyte dysfunction (6, 7).

The clinical and metabolic phenotype of PKU is highly heterogeneous and largely determined by residual phenylalanine hydroxylase activity. Lower residual enzyme activity is typically associated with higher blood phenylalanine levels and more severe manifestations in the absence of treatment(8).

Beyond its well-established neurological effects, increasing evidence suggests that chronic hyperphenylalaninemia may also affect ocular structures and visual function. Dopamine, synthesized from phenylalanine-derived tyrosine, plays a key role in retinal signaling and regulation of eye growth. Altered dopaminergic pathways have been implicated in the development of myopia and visual dysfunction in experimental models of PKU, providing a plausible mechanistic link between metabolic imbalance and ocular involvement (9). Nevertheless, available data on ocular abnormalities in PKU—including iris and retinal hypopigmentation, cataract formation, corneal opacities, and functional visual

impairment—remain limited and fragmented, particularly in pediatric populations receiving early dietary treatment (10) .

Accordingly, the present study aimed to evaluate ocular findings in children with early-treated PKU diagnosed through neonatal or selective screening and to examine the association between ophthalmological manifestations and serum phenylalanine levels in this population.

Patients and Methods

This cross-sectional study included 33 pediatric patients diagnosed with phenylketonuria (PKU) through neonatal or selective screening who were attending the Genetics and Metabolic Outpatient Clinic at Mansoura University Children's Hospital (MUCH). Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment.

Eligible participants were children aged 3–18 years with a confirmed diagnosis of PKU who were under regular follow-up at the metabolic unit of MUCH. Newborn screening was performed using dried blood spot samples collected on Whatman® 903 filter paper from heel-stick blood between the third and seventh days of life. Samples were processed according to the NeoBase™ non-derivatized tandem mass spectrometry (MS/MS) kit protocol and analyzed using the TQD MS/MS system. The screening panel included phenylalanine, tyrosine, and acylcarnitines. Positive screening results were confirmed by plasma amino acid analysis using chromatography to quantify phenylalanine levels (11).

Exclusion Criteria:

- Children aged below 3 or above 18 years.
- History of systemic disease known to affect the retina e.g., diabetes.
- History of other ocular disease, previous ocular trauma or operation.
- History of any neurological disease unrelated to PKU.
- Prematurity < 36 weeks of gestational age.
- Interfering medical treatment.

Ophthalmological examination

All participants underwent comprehensive ophthalmological evaluation at the Mansoura Ophthalmology Center, Mansoura University. Examinations included:

- Measurement of visual acuity using age-appropriate Snellen charts, with values converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis
- Refractive assessment when indicated, based on objective cycloplegic refraction using a conventional autorefractometer
- Measurement of intraocular pressure using a non-contact tonometer

- Detailed anterior segment examination using slit-lamp biomicroscopy
- Dilated fundus examination using slit-lamp biomicroscopy with direct and indirect ophthalmoscopy
- Assessment of ocular motility

Ethical consideration

The study was approved by Institutional Review Board, Mansoura Faculty of Medicine, Mansoura University. Code Number:R.23.12.2432

Statistical analysis:

Mean and standard deviation of all parameters in serum will be calculated. Student t-test will be used for comparison of means and $p < 0.05$ will be considered significant for parametric data. Wilcoxon test will be used for non-parametric data,

And $p < 0.05$ will be considered significant. Descriptive statistics were used to analyze demographic data and phenylalanine levels. The relationship between phenylalanine levels and ocular findings was assessed using correlation analysis. Prognostic value was determined using receiver operating characteristic (ROC) curve analysis.

Results

1. Demographic and Biochemical Characteristics

A total of 33 children with phenylketonuria (PKU) were included.

The cohort consisted of 13 males (39%) and 20 females (61%), with a female-to-male ratio of 1.5:1 ($p = 0.50$). The mean age was 5.6 ± 2.1 years. Median serum phenylalanine (Phe) level was 433 µmol/L (range 110–1250 µmol/L).

2. General Ophthalmic Findings

Ophthalmological abnormalities involving both anterior and posterior segments were identified in a proportion of the studied patients. Corneal clouding was observed in 5 children (15.2%), iris hypopigmentation in 4 (12.1%), retinal hypopigmentation in 11 (33.3%), and posterior polar cataract in 3 patients (9.1%). Optic disc abnormalities, including disc pallor or myopic disc appearance, were detected in 5 children (15.2%).

Refractive errors were identified in 8 patients (24.2%), including myopia (n = 5) and astigmatism (n = 3). Ocular motility abnormalities (eso- or exotropia) were present in 4 patients (12.1%). Intraocular pressure measurements were within normal limits in all examined children (Table 1 **and** Fig. 1).

Rare findings such as vitreous floaters and retinal vascular tortuosity were observed in single cases and were therefore interpreted descriptively.

Table 1
General ocular findings among PKU patients

Ocular Finding	Normal n (%)	Abnormal n (%)	Abnormality Type	p-value
Cornea	28 (84.8%)	5 (15.2%)	Clouding	0.003
Iris	29 (87.9%)	4 (12.1%)	Hypopigmentation	0.001
Vitreous	32 (97%)	1 (3%)	Floaters	------*
Retina	22 (66.7%)	11 (33.3%)	Hypopigmentation	0.273
Retinal Vessels	32 (97%)	1 (3%)	Tortuosity	------*
Lens	30 (90.9%)	3 (9.1%)	Posterior polar cataract	< 0.001
Optic Disc	28 (84.8%)	5 (15.2%)	Disc pallor or myopic disc	0.003
Refractive Error	25 (75.8%)	8 (24.2%)	Myopia (n = 5), Astigmatism (n = 3)	0.047
Ocular Motility	29 (87.9%)	4 (12.1%)	Eso-/Exotropia	< 0.001
IOP	33 (100%)	0	—	—

* interpreted descriptively as number of abnormalities in one group were less than 2 cases

3. Relationship Between Phenylalanine Levels and Specific Ocular Findings

Median Phe concentrations were compared between normal and abnormal Median serum phenylalanine concentrations were compared between children with normal and abnormal findings for each ocular structure (Table 2). Higher median Phe levels were observed among patients with corneal clouding, cataract, retinal hypopigmentation, optic disc abnormalities, and refractive errors compared with those without these findings. The differences were statistically significant for corneal involvement ($p = 0.026$), cataract ($p = 0.006$), retinal hypopigmentation ($p < 0.001$), optic disc abnormalities ($p = 0.005$), and refractive errors ($p = 0.040$). Associations involving very infrequent abnormalities were not statistically emphasized due to limited event numbers.

Table 2
Specific ocular findings and phenylalanine relationship

Ocular Structure	Normal Phe (µmol/L)	Abnormal Phe (µmol/L)	p-value
Cornea	208.5 (110–1250)	1020 (530–1145)	0.026
Iris	216 (110–1250)	1010 (637–1040)	0.80
Lens (Cataract)	302 (110–1200)	1145 (1040–1250)	0.006
Retina	195 (110–1145)	1020 (523–1250)	< 0.001
Retinal Vessels	411 (110–1250)	1200	0.121
Vitreous	411 (110–1200)	1250	0.061
Refractive Error	200 (110–1200)	1020 (201–1250)	0.040
Optic Disc	208 (110–1250)	1090 (600–1180)	0.005

Figure 2. Median serum phenylalanine levels in children with normal versus abnormal ocular findings. Across corneal, lenticular, retinal, and optic disc assessments, higher phenylalanine concentrations were observed in participants with abnormal findings. Values are presented as median µmol/L.

4. Predictive Value of Phenylalanine for Ocular Pathology (ROC Analysis)

Receiver operating characteristic (ROC) curve analysis was performed to explore the discriminative ability of serum phenylalanine levels for selected ocular abnormalities **(**Table 3 **and Fig. 3).** Phenylalanine demonstrated moderate to high discriminative performance for corneal clouding (AUC = 0.81), retinal hypopigmentation (AUC = 0.88), and optic disc abnormalities (AUC = 0.88), and high discriminative performance for cataract (AUC = 0.94).

Cutoff values around 500 µmol/L were associated with increased probability of corneal and retinal abnormalities, while values exceeding 1000 µmol/L were associated with lens and optic disc involvement. Given the sample size, these thresholds should be interpreted as exploratory.

Table 3
ROC Performance of Phenylalanine for Predicting Ocular Abnormalities

Ocular Outcome	AUC	95% CI	p-value	Optimal Cutoff (µmol/L)	Sensitivity	1–Specificity
Corneal Clouding	0.811	0.666–0.956	0.029	501	100%	36%
Iris Hypopigmentation	0.784	0.636–0.932	0.069	501	100%	38%
Cataract	0.944	0.861–1.000	0.012	1020	100%	13.3%
Retinal Hypopigmentation	0.884	0.883–1.000	< 0.001	501	100%	18%
Optic Disc Abnormality	0.879	0.753–1.000	0.008	1020	80%	10.7%

Figure 3. Receiver operating characteristic (ROC) curves illustrating the discriminative performance of serum phenylalanine levels for selected ocular abnormalities in children with phenylketonuria. Curves are shown for corneal clouding, cataract, retinal hypopigmentation, and iris hypopigmentation. The area under the curve (AUC) reflects the ability of phenylalanine levels to distinguish between children with and without each ocular finding. The diagonal line represents no discriminative performance (AUC = 0.5).

5. Correlation Analysis

Higher serum phenylalanine levels were significantly correlated with worse visual acuity, expressed as higher logMAR values (Spearman r = 0.843, p < 0.001). Correlations between phenylalanine levels and axial length or keratometric parameters (K1 and K2) did not reach statistical significance.

Parameter	Correlation (Spearman r)	p-value
Visual Acuity	0.843	< 0.001
K1	0.400	0.505
K2	0.400	0.505
Axial Length	0.700	0.188

Discussion

The present study demonstrates that ocular abnormalities are relatively common among children with phenylketonuria (PKU), and many of these findings—including corneal clouding, iris and retinal hypopigmentation, posterior polar cataract, optic disc abnormalities, refractive errors, and strabismus—show strong associations with elevated serum phenylalanine (Phe) levels. Recent literature increasingly recognizes the eye as an early metabolic sensor in PKU, paralleling the CNS in its susceptibility to

phenylalanine toxicity (9, 12). Our findings are consistent with this evolving understanding and further expand the evidence linking metabolic control to ocular integrity.

Pigmentary changes were particularly prominent in children with higher Phe levels. Modern mechanistic studies show that excess phenylalanine disrupts melanin biosynthesis by reducing tyrosine availability and directly inhibiting tyrosinase and related melanogenic enzymes(13, 14). Clinical observations in contemporary PKU cohorts confirm that iris and retinal hypopigmentation remain more common in individuals with suboptimal metabolic control(9) .The strong relationship between Phe and hypopigmentation in our dataset supports these biochemical and clinical findings and highlights melanin pathways as a sensitive metabolic target.

Retinal and optic nerve abnormalities observed in our cohort are also strongly supported by recent imaging and functional studies. High-resolution OCT studies from the past five years report significant thinning of the peripapillary retinal nerve fiber layer (RNFL), reduced ganglion cell–inner plexiform layer (GCIPL), and microstructural neuroretinal changes in PKU patients—particularly in those with elevated lifetime or current Phe levels(15–18). Functional studies show reduced contrast sensitivity, delayed visual processing, and abnormal visual evoked potentials in poorly controlled patients (10, 19). Our findings of retinal hypopigmentation, optic disc pallor, and a strong correlation between Phe and reduced visual acuity closely align with this recent evidence, suggesting that ocular neurodegeneration in PKU is both structural and functional in nature.

Lens involvement also showed a clear link to metabolic control. While cataract in PKU has traditionally been described in older literature(13), recent reports continue to note lens opacities in children with severe or fluctuating hyperphenylalaninemia(20). Oxidative stress from phenylalanine derivatives and metabolic lens vulnerability remains the leading hypotheses(21). In our cohort, cataract occurred exclusively in children with very high Phe levels, and phenylalanine demonstrated excellent predictive discrimination (AUC 0.94), providing one of the most robust quantitative validations of this association.

Refractive errors and strabismus were also significantly associated with higher Phe levels in our patients. Recent developmental-visual studies indicate that abnormal retinal signaling, impaired dopamine pathways, and altered visual cortex maturation in PKU may contribute to refractive instability and ocular misalignment(22–24) .Our results are consistent with this work and indicate that mild-to-moderate metabolic dysregulation during critical periods of visual development may be sufficient to disrupt emmetropization and ocular motor control.

One of the most important contributions of this study is the derivation of phenylalanine cutoff values associated with multiple ocular abnormalities using ROC analysis. To our knowledge, no recent PKU studies have quantified specific phenylalanine thresholds for corneal, lenticular, retinal, and optic nerve changes within a single cohort. Our data support a multi-tiered model whereby ocular risk rises significantly above 500 µmol/L and becomes high above 1000 µmol/L—information that has not been provided in previous ophthalmic or metabolic studies.

Together, our findings reveal a consistent, multi-tissue dose–response pattern: as phenylalanine levels rise, abnormalities appear progressively across corneal, pigmentary, lenticular, retinal, and optic nerve structures. Earlier studies examined each structure in isolation, but our integrated dataset demonstrates that the entire eye behaves as a metabolically sensitive organ. This unified pattern supports the development of ophthalmic screening strategies tailored to phenylalanine levels and may assist clinicians in identifying patients who require more frequent ocular monitoring.

In summary, this study confirms that ocular involvement in PKU is metabolically driven, clinically meaningful, and detectable even in childhood. Elevated phenylalanine was consistently linked to structural abnormalities and functional visual loss. By integrating detailed ophthalmic evaluation with quantitative ROC-based phenylalanine thresholds, our study introduces novel evidence that may improve targeted ophthalmic surveillance and support more stringent metabolic management to prevent long-term visual morbidity in children with PKU.

Conclusion

Ocular abnormalities are common and multisystemic in children with phenylketonuria and are associated with increasing serum phenylalanine levels. Exploratory analyses suggest that phenylalanine concentrations above approximately 500 µmol/L are associated with an increased likelihood of ocular involvement, with more severe abnormalities observed at levels exceeding 1000 µmol/L. These findings support the eye as a metabolically sensitive organ and highlight the potential value of phenylalanine-guided ophthalmic surveillance in pediatric PKU.

STUDY LIMITATION and FUTURE DIRECTIONS

This study’s cross-sectional design and single-center cohort limit causal inference and generalizability. Visual assessments were sometimes challenging in younger children, and detailed imaging was not available for all participants. Longitudinal studies are needed to track the progression of ocular changes in PKU and evaluate the impact of early and sustained metabolic control. Advanced imaging and functional assessments could further clarify structure–function relationships, while multicenter studies may validate phenylalanine thresholds for risk stratification and guide personalized ophthalmic screening protocols

Abbreviations

PKU
Phenylketonuria
Phe
Phenylalanine
ROC
Receiver Operating Characteristic

AUC
Area Under the Curve
IOP
Intraocular Pressure
logMAR
Logarithm of the Minimum Angle of Resolution
MS/MS
Tandem Mass Spectrometry
PAH
Phenylalanine Hydroxylase
MHP
Mild Hyperphenylalaninemia
cPKU
Classical Phenylketonuria
mPKU
Mild Phenylketonuria
MUCH
Mansoura University Children's Hospital
MOC
Mansoura Ophthalmology Center

Declarations

Ethical approval :This study was conducted by the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Research Ethics Committee of Faculty of Medicine, Mansoura University (Code Number :R.23.12.2432) and followed by Institutional Research Board. Informed consents were obtained from all parents of the children included in this study.

Consent to participate : informed consent was obtained from all patient caregivers before inclusion in the study.

Clinical trial number: Not applicable

Consent for publication: Not Applicable

Data availability: The datasets generated and/or analyzed during the current study are not publicly available due to institutional and ethical restrictions but are available from the corresponding author on reasonable request

Conflict of interest:The authors declare that no conflicts of interest associated with this manuscript.

Research funding: the authors declare that no funds ,grants, or other support were received during the preparation of this research .**Author contributions**:

H.E. contributed to patient recruitment, clinical metabolic assessment, data collection, and drafted the initial manuscript.

D.L. performed comprehensive ophthalmological examinations and contributed to data acquisition and interpretation.

M.A.H. conceptualized and designed the study, performed statistical analysis, supervised the research process, contributed to data interpretation, and critically revised the manuscript for important intellectual content.

All authors approved the final manuscript and agreed to be accountable for all aspects of the work

Acknowledgments: The authors would like to thank the children and their families for their participation in this study. We also acknowledge the nursing staff and laboratory personnel at Mansoura University Children's Hospital and Mansoura ophthalmology center for their assistance in patient coordination and biochemical assessments.

References

1. Waisbren SE, Noel K, Fahrbach K, Cella C, Frame D, Dorenbaum A, et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mol Genet Metab. 2007;92(1–2):63–70.
2. Tomm A, Thiele AG, Rohde C, Kirmse S, Kiess W, Beblo S. Executive functions & metabolic control in phenylketonuria (PKU) and mild hyperphenylalaninemia (mHPA). Mol Genet Metab. 2024;143(1–2):108544.
3. Walter JH, White FJ, Hall SK, MacDonald A, Rylance G, Boneh A, et al. How practical are recommendations for dietary control in phenylketonuria? Lancet. 2002;360(9326):55–7.
4. Moat SJ, Schulenburg-Brand D, Lemonde H, Bonham JR, Weykamp CW, Mei JV, et al. Performance of laboratory tests used to measure blood phenylalanine for the monitoring of patients with phenylketonuria. J Inherit Metab Dis. 2020;43(2):179–88.
5. Camp KM, Parisi MA, Acosta PB, Berry GT, Bilder DA, Blau N et al. Phenylketonuria Scientific Review Conference: state of the science and future research needs. Mol Genet Metab. 2014;112(2):87–122.
6. van Vliet D, van der Goot E, van Ginkel WG, van Faassen HJR, de Blaauw P, Kema IP, et al. The increasing importance of LNAA supplementation in phenylketonuria at higher plasma phenylalanine concentrations. Mol Genet Metab. 2022;135(1):27–34.
7. Rondelli V, Koutsioubas A, Di Cola E, Fragneto G, Grillo I, Del Favero E, et al. Dysmyelination and glycolipid interference caused by phenylalanine in phenylketonuria. Int J Biol Macromol. 2022;221:784–95.

8. Himmelreich N, Shen N, Okun JG, Thiel C, Hoffmann GF, Blau N. Relationship between genotype, phenylalanine hydroxylase expression and in vitro activity and metabolic phenotype in phenylketonuria. Mol Genet Metab. 2018;125(1–2):86–95.
9. Hopf S, Nowak C, Hennermann JB, Schmidtmann I, Pfeiffer N, Pitz S. Saccadic reaction time and ocular findings in phenylketonuria. Orphanet J Rare Dis. 2020;15(1):124.
10. Gramer G, Forl B, Springer C, Weimer P, Haege G, Mackensen F, et al. Visual functions in phenylketonuria-evaluating the dopamine and long-chain polyunsaturated fatty acids depletion hypotheses. Mol Genet Metab. 2013;108(1):1–7.
11. Guo K, Zhou X, Chen X, Wu Y, Liu C, Kong Q. Expanded Newborn Screening for Inborn Errors of Metabolism and Genetic Characteristics in a Chinese Population. Front Genet. 2018;9:122.
12. Anwar MS, Waddell B, O'Riordan J. Neurological improvement following reinstitution of a low phenylalanine diet after 20 years in established phenylketonuria. BMJ Case Rep. 2013;2013.
13. Zwaan J. Eye findings in patients with phenylketonuria. Arch Ophthalmol. 1983;101(8):1236–7.
14. Nulmans I, Lequeue S, Desmet L, Neuckermans J, De Kock J. Current state of the treatment landscape of phenylketonuria. Orphanet J Rare Dis. 2025;20(1):281.
15. Serfozo C, Barta AG, Horvath E, Sumanszki C, Csakany B, Resch M, et al. Altered visual functions, macular ganglion cell and papillary retinal nerve fiber layer thickness in early-treated adult PKU patients. Mol Genet Metab Rep. 2020;25:100649.
16. Serfozo C, Barta AG, Horvath E, Sumanszki C, Csakany B, Resch M, et al. Reduced macular thickness and macular vessel density in early-treated adult patients with PKU. Mol Genet Metab Rep. 2021;27:100767.
17. Buonamassa R, Boscia G, Gaudiomonte M, Guerriero S, Fischetto R, Montepara A, et al. Neurovascular retinal impairment in early-treated adults with phenylketonuria. Front Neurol. 2024;15:1305984.
18. Lotz-Havla AS, Weiss K, Schiergens K, Regenauer-Vandewiele S, Parhofer KG, Christmann T, et al. Optical Coherence Tomography to Assess Neurodegeneration in Phenylalanine Hydroxylase Deficiency. Front Neurol. 2021;12:780624.
19. Diamond A, Herzberg C. Impaired sensitivity to visual contrast in children treated early and continuously for phenylketonuria. Brain. 1996;119(Pt 2):523–38.
20. Seyyar SA, Soysal GG, Hopurcuoglu D. Pediatric phenylketonuria and the eye: Unveiling subclinical anterior segment changes. Indian J Ophthalmol. 2025;73(12):1847.
21. Ribas GS, Sitta A, Wajner M, Vargas CR. Oxidative stress in phenylketonuria: what is the evidence? Cell Mol Neurobiol. 2011;31(5):653–62.
22. Zhou X, Pardue MT, Iuvone PM, Qu J. Dopamine signaling and myopia development: What are the key challenges. Prog Retin Eye Res. 2017;61:60–71.
23. Tian T, Zou L, Wang S, Liu R, Liu H. The Role of Dopamine in Emmetropization Modulated by Wavelength and Temporal Frequency in Guinea Pigs. Invest Ophthalmol Vis Sci. 2021;62(12):20.

24. Bergen MA, Park HN, Chakraborty R, Landis EG, Sidhu C, He L, et al. Altered Refractive Development in Mice With Reduced Levels of Retinal Dopamine. Invest Ophthalmol Vis Sci. 2016;57(10):4412–9.

Figures

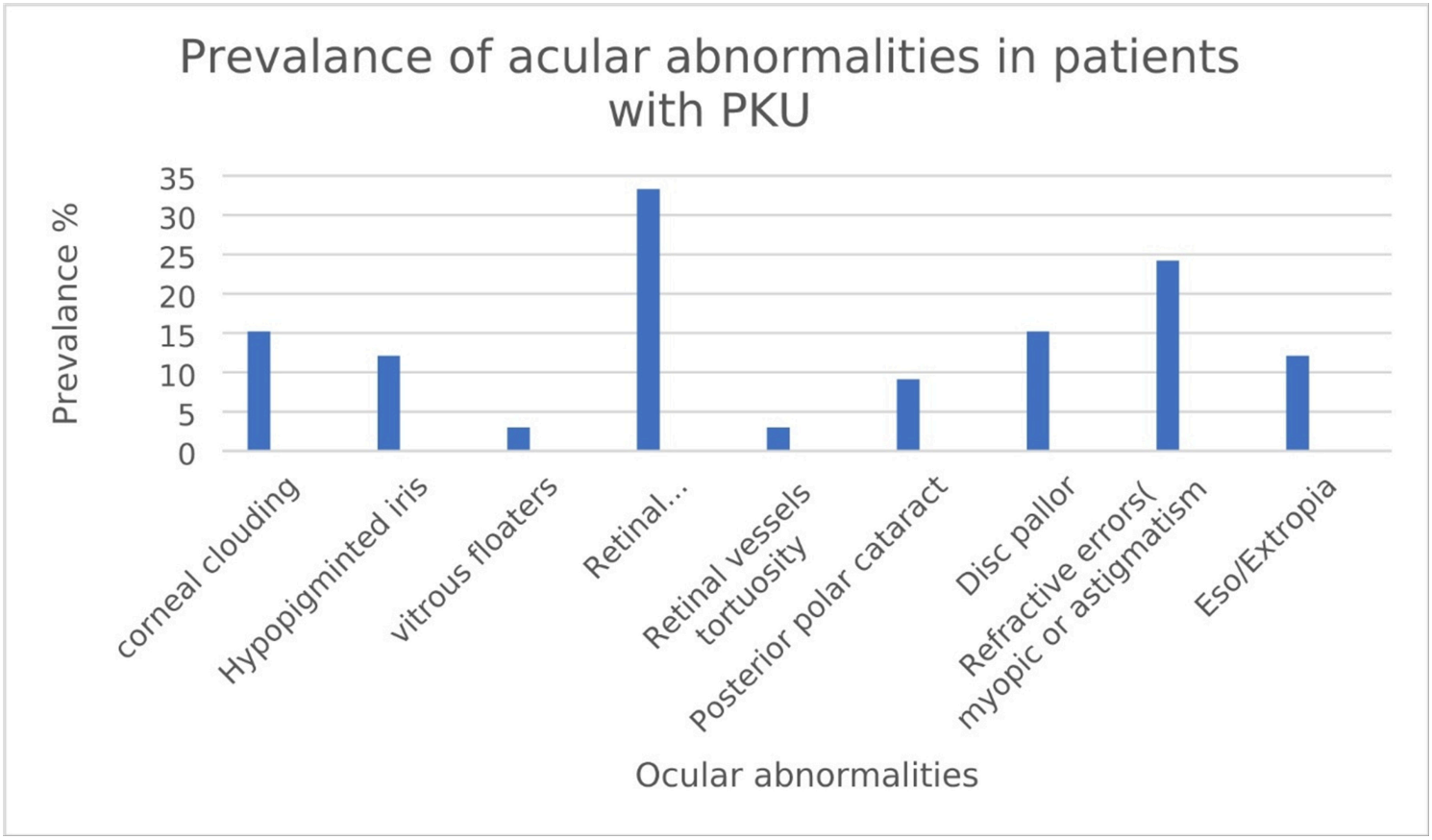


Figure 1

Prevalence of ocular abnormalities in children with phenylketonuria. Retinal hypopigmentation and refractive errors were the most frequent findings

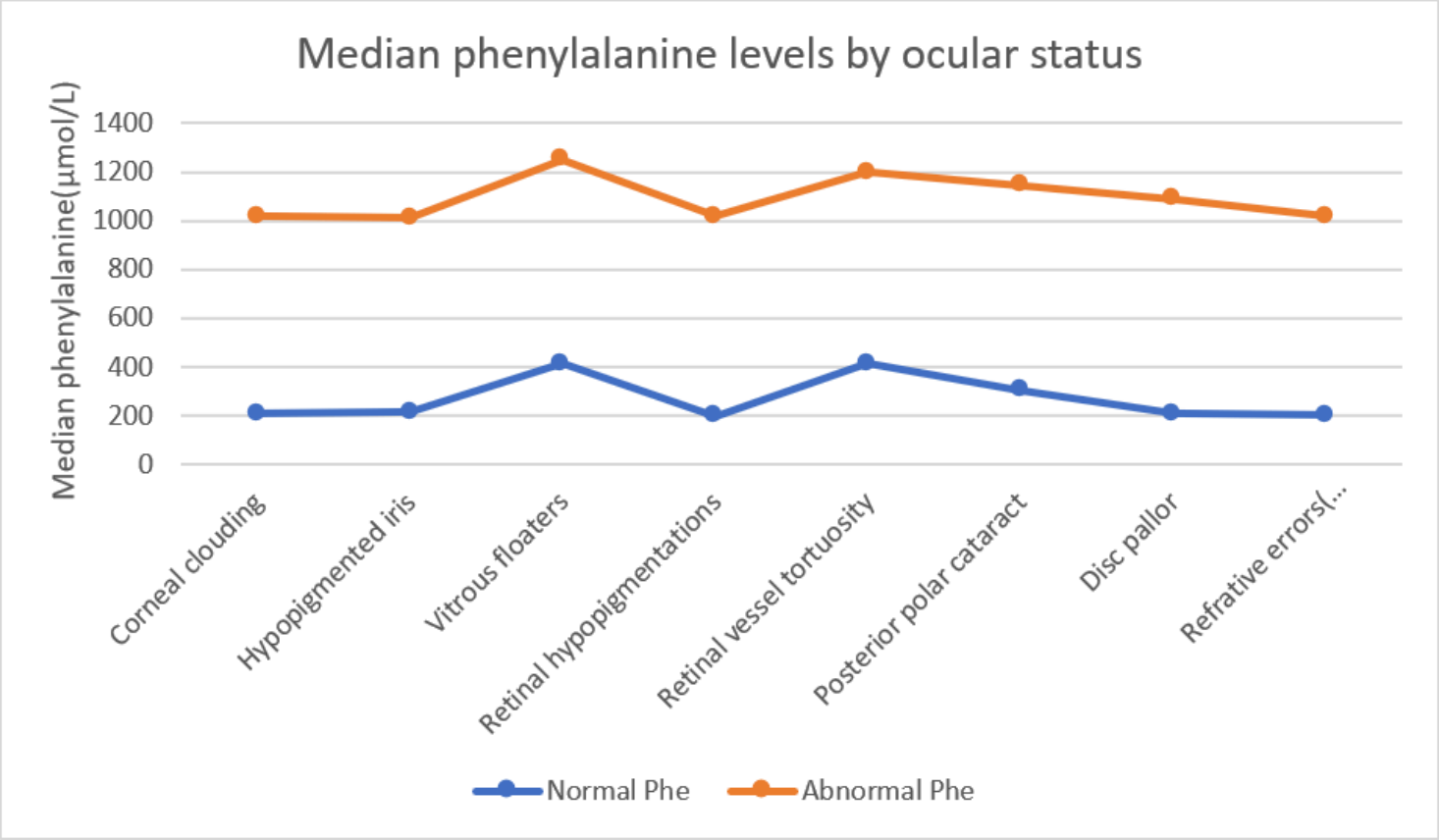


Figure 2

Median phenylalanine levels by ocular status

Median serum phenylalanine levels in children with normal versus abnormal ocular findings. Across corneal, lenticular, retinal, and optic disc assessments, higher phenylalanine concentrations were observed in participants with abnormal findings. Values are presented as median µmol/L.

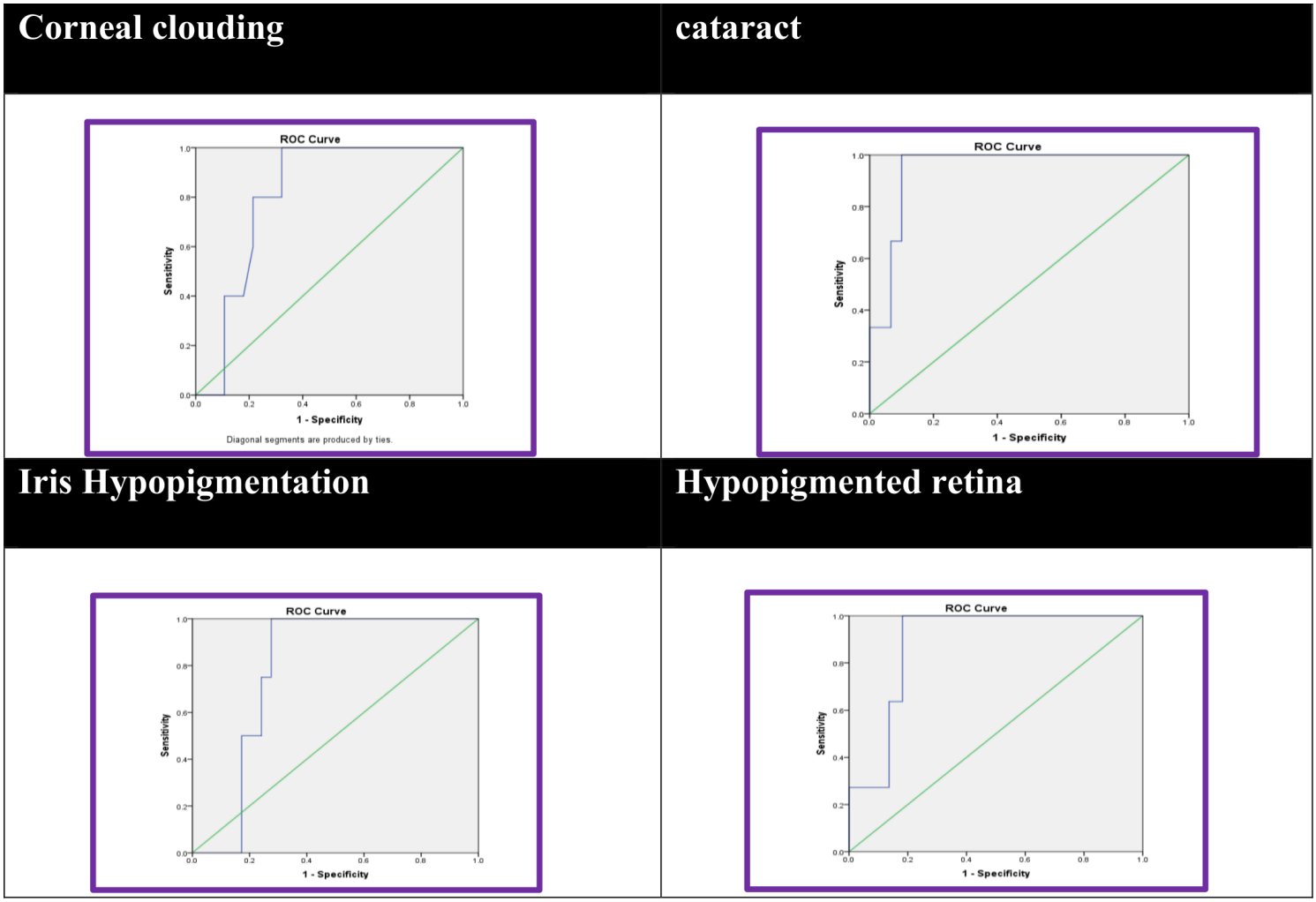


Figure 3

Receiver operating characteristic (ROC) curves illustrating the discriminative performance of serum phenylalanine levels for selected ocular abnormalities in children with phenylketonuria. Curves are shown for corneal clouding, cataract, retinal hypopigmentation, and iris hypopigmentation. The area under the curve (AUC) reflects the ability of phenylalanine levels to distinguish between children with and without each ocular finding. The diagonal line represents no discriminative performance (AUC = 0.5).