• Clinical Research •

Identifying predictors of visual improvement in ethambutol optic neuropathy: insights from a 5-year retrospective analysis in a tertiary clinic in Indonesia

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Abstract

• **AIM:** To characterize the demographic and clinical features of ethambutol optic neuropathy (EON) in an Indonesian patient population and explore prognostic factors for visual recovery.

• **METHODS:** Retrospective study of 58 EON patients at an Indonesian eye center (2017-2022). Demographics, ethambutol treatment, ophthalmologic findings were collected. Visual outcomes after ethambutol cessation assessed at 3-12mo. Patients categorized as having visual improvement (≥2 Snellen lines and/or >5° visual field gain) or no improvement.

• **RESULTS:** Mean age was 55.5±12.9y, with 56.9% females. Median duration of ethambutol use was 9mo (range: 2-20) at a mean daily dose of 19.7±5.3 mg/kg. At presentation, mean visual acuity was 1.3 logMAR (range: 0-2.5), with normal fundus appearance in 72.4% of eyes. The most common visual field defect was generalized depression (52.4%). After ethambutol cessation, 56.9% of patients had visual improvement. Younger age (50.24±13.8y *vs* 62.14±8.9y, *P*<0.01), lower ethambutol dose (17.3±5 *vs* 23.3±2.9 mg/kg·d, *P*<0.01), shorter treatment duration (6.79±2.6mo *vs* 10.27±1.2mo, *P*<0.01), and absence of hypertension (16% *vs* 83%, *P*=0.012) or kidney disease (0 *vs* 83%, *P*<0.01) were associated with higher likelihood of visual improvement. Diabetes did not differ between groups (*P*=0.889).

• **CONCLUSION:** Over half experience visual recovery after ethambutol cessation. Younger age, lower cumulative dose, absence of hypertension or kidney disease predict better visual outcomes.

• **KEYWORDS:** ethambutol optic neuropathy; visual recovery; prognostic factors; tuberculosis
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INTRODUCTION

Ethambutol, one of the drugs used in tuberculosis treatment regimen is known to cause optic neuropathy in 1%-5% of patients at doses of 15-25 mg/kg·d for at least two months[1-3]. Ethambutol optic neuropathy (EON) typically presents as bilateral, painless, gradual vision loss with central or cecocentral scotomas, impaired color vision, and potentially irreversible visual deficits[4-6]. The mechanism of toxicity is thought to involve impaired mitochondrial function and retinal ganglion cell damage[7-8].

In Indonesia, the high tuberculosis burden and limited monitoring during treatment pose challenges in preventing EON[9]. The lack of a standardized screening protocol and reliance on visual acuity alone may lead to delayed diagnosis and poorer outcomes[10]. Incorporation of ancillary tests such as optical coherence tomography (OCT), visual evoked potentials (VEP), and electroretinography (ERG) can improve early detection of EON[11-14], but these modalities are not widely available in primary care settings where tuberculosis patients are routinely managed.

Color vision assessment, using tests such as Ishihara plates or the Farnsworth D-15, is a simple, rapid, and inexpensive method that can detect EON-associated dyschromatopsia

before visual acuity is affected[15-16]. Implementing color vision screening during monthly tuberculosis treatment visits in primary care could potentially improve early EON detection and facilitate prompt referral to ophthalmologists for further evaluation and management[17].

While several risk factors for developing EON have been identified, including older age, higher ethambutol dose, and longer treatment duration[18-21], the prognostic factors influencing visual recovery after ethambutol discontinuation remain poorly understood[22-24]. Identifying predictors of visual improvement could guide medication dosing, monitoring, and patient counselling in EON management.

This study aimed to characterize the demographic and clinical profile of EON in an Indonesian patient population, identify prognostic factors for visual recovery, and explore the potential role of color vision screening in the early detection and management of EON in primary care settings. We hypothesized that younger age, lower ethambutol dose and shorter treatment duration, better presenting visual acuity, and absence of comorbidities such as hypertension and renal impairment would be associated with a higher likelihood of visual improvement after ethambutol cessation. Additionally, we anticipated that the incorporation of regular color vision testing into routine tuberculosis treatment monitoring could enhance early EON detection and improve visual outcomes by facilitating timely intervention.

Understanding the clinical features, risk factors, and predictors of recovery in EON is crucial for developing evidence-based screening and management strategies to prevent permanent vision loss from this serious complication of tuberculosis therapy. Furthermore, evaluating the feasibility and effectiveness of color vision testing in primary care could inform the design and implementation of practical, low-cost interventions to improve EON detection and outcomes in resource-limited settings with a high tuberculosis burden, such as Indonesia.

PARTICIPANTS AND METHODS

Ethical Approval This retrospective, single-center study was conducted at JEC Eye Hospitals and Clinics in Indonesia. The study protocol was approved by the Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Ethics approval was obtained from the Medical and Health Research Ethics Committee of Universitas Gajah Mada under reference number KE/FK/1266/EC/2022, valid from October 5, 2022 to October 5, 2023. Informed consent was waived due to the retrospective nature of the study.

Study Design and Population The electronic medical records database was searched to identify patients diagnosed with EON between January 2017 and January 2022. EON was diagnosed based on a history of progressive, bilateral visual impairment with dyschromatopsia and/or visual field defects following at least one month of ethambutol treatment, after exclusion of other potential etiologies. All patients meeting the diagnostic criteria were included, regardless of age, sex, or tuberculosis characteristics. Patients with incomplete medical records, pre-existing ocular conditions (*e.g.*, glaucoma, retinal disorders, optic neuropathies), or <3mo follow-up after ethambutol cessation were excluded.

Data Collection Demographic information, including age, sex, weight, and medical comorbidities (diabetes, hypertension, kidney disease), was extracted from the medical records. Ethambutol treatment details, such as daily dose and duration of therapy, were noted. The results of comprehensive ophthalmic examinations at initial and follow-up visits were recorded, including best-corrected visual acuity (BCVA), color vision (Ishihara plates), slit-lamp findings, fundus appearance, and visual field parameters (Humphrey Field Analyzer, 24-2 SITA Standard protocol). When available, spectral-domain optical coherence tomography (OCT) measurements of peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell-inner plexiform layer (GC-IPL) thickness, fundus photography, and pattern VEP findings were also collected.

Outcome Measures and Statistical Analysis The primary outcome was the proportion of patients achieving visual improvement, defined as an increase in BCVA of ≥2 Snellen lines and/or expansion of visual field by >5° in at least one eye, at 3-12mo after discontinuing ethambutol. Patients were categorized as having visual improvement or no visual improvement based on this criterion.

Statistical Analysis Descriptive statistics were used to summarize patient characteristics and ophthalmologic findings. Continuous variables were expressed as mean±standard deviation or median (range), while categorical data were presented as frequencies and percentages. Demographics, ethambutol parameters, and comorbidities were compared between the visual improvement and no improvement groups using the independent *t*-test or Mann-Whitney *U* test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables, as appropriate. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Characteristics A total of 87 patients with presumed EON were identified through a retrospective chart review at JEC Eye Hospital between January 2017 and January 2022. After applying the inclusion and exclusion criteria, 58 patients (116 eyes) were included in the final analysis (Figure 1).

The mean age was 55.5±12.9y, and there was a slight female predominance (56.9%). Most patients (74.1%) reported a

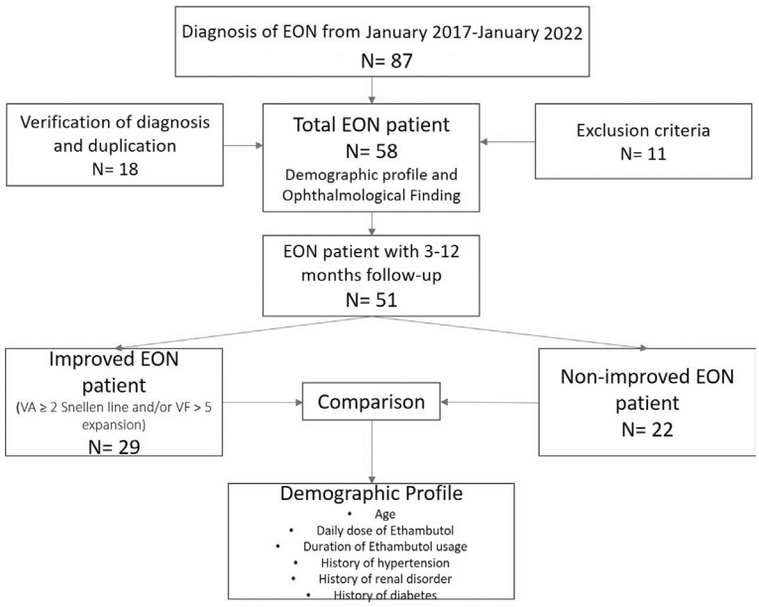

Figure 1 Patient selection and study flowchart EON: Ethambutol optic neuropathy.

gradual onset of visual symptoms, which included blurred vision, difficulty reading, dyschromatopsia, and impaired driving. The mean daily ethambutol dose was 19.7±5.3 mg/kg, and the median duration of treatment prior to symptom onset was 9mo (range: 2-20; Table 1).

Ophthalmologic Findings At presentation, the mean best-corrected visual acuity (BCVA) was 1.3 logMAR (Snellen equivalent 20/400), with a range of 0 to 2.5 logMAR (Table 2). Automated perimetry (24-2 SITA Standard) demonstrated diffuse visual field depression, with a mean deviation of -13.4 dB (range: -33.6 to -1.0) and a mean pattern standard deviation of 5.9±2.7 dB. OCT analysis revealed a mean average peripapillary RNFL thickness of 99.87±19.8 μm and a mean average macular GC-IPL thickness of 77 μm (range: 27-94). Fundus examination was normal in 72.4% of eyes, while disc margin blurring, diffuse atrophy, and temporal pallor were noted in 20.7%, 3.4%, and 3.4% of eyes, respectively. Among 103 eyes with reliable visual fields, the most common patterns were generalized depression (52.4%), central scotoma (26.2%), and hemianopia (12.6%). Four eyes underwent pattern VEP testing, all of which showed reduced amplitude and prolonged latency of the P100 waveform.

Visual Outcomes and Prognostic Factors Fifty-one patients (102 eyes) had at least 3mo of follow-up after ethambutol cessation, with a median duration of 7mo (range: 3-12; Table 1). Visual improvement, defined as a gain of ≥2 Snellen lines and/or >5° of visual field expansion in at least one eye, was observed in 29 patients (56.9%), while 22 patients (43.1%) showed no improvement (Table 2). Patients with visual improvement were significantly younger (50.24±13.8 *vs* 62.14±8.9y, $P<0.01$), had a lower mean daily ethambutol dose (17.3±5.0 *vs* 23.3±2.9 mg/kg, $P<0.01$), and a shorter median duration of treatment (6.79±2.6 *vs* 10.27±1.2mo, $P<0.01$). The proportion of patients with hypertension (16% *vs* 83%, $P=0.012$) and kidney disease (0 *vs* 83%, $P<0.01$) was also significantly lower in the visual improvement group. The prevalence of diabetes did not differ between the two groups ($P=0.889$).

Eyes with visual improvement had a better mean presenting BCVA compared to those without improvement (1.15 *vs* 1.4 logMAR, $P=0.029$). At the last follow-up, the mean BCVA was 0.3 logMAR (Snellen equivalent 20/40) in the improved group and 1.3 logMAR (Snellen equivalent 20/400) in the non-improved group ($P<0.01$). There was a positive correlation between initial and final BCVA ($r=0.564$, $P<0.001$). Notably, all 6 eyes with optic disc atrophy or temporal pallor at presentation were in the non-improved group.

This study identified several baseline characteristics and ocular findings associated with a higher likelihood of visual recovery in EON. Younger age, lower ethambutol dose, shorter treatment duration, absence of hypertension or kidney disease, and better presenting BCVA were significant predictors of visual improvement. The presence of optic atrophy or temporal pallor at initial examination was associated with a poor prognosis.

DISCUSSION

This retrospective study aimed to characterize the demographic and clinical features of EON in an Indonesian population and identify prognostic factors for visual recovery. The mean age of our cohort (55.5±12.9y) was comparable to that reported by Lee *et al*[5] (58.23±16.68y) but younger than the patients in Chen *et al*'s[11] study (70.02±14.26y). The mean daily ethambutol dose in our study was 19.7±5.3 mg/kg, which is higher than the recommended maximum of 15 mg/kg·d[8,21].

Table 1 Demographic characteristics of ethambutol optic neuropathy patient with and without visual improvement (follow up 3-12mo)

Characteristics	Visual improvement (*n*=29)	No visual improvement (*n*=22)	*P*
Age (y)	50.24±13.8	62.14±8.9	<0.01
Gender (male/female)	13/16	9/13	0.078
Ethambutol duration (mo)	6.79±2.6	10.27±1.2	<0.01
Ethambutol daily dosage (mg/kg)	17.3±5	23.3±2.9	<0.01
Hypertension (yes/no)	4/25	10/12	0.012
Kidney disease (yes/no)	0/29	10/12	<0.01
Diabetes (yes/no)	10/19	8/14	0.889
Follow up time (mo)	9 (3-12)	6 (3-12)	-
Initial VA (logMAR)	1.15 (0.1-2.5)[a]	1.4 (0-2.2)[b]	0.029
Final VA (logMAR)	0.3 (0-3)[a]	1.3 (0.3-3)[b]	<0.01

[a]*n*=58 eyes, [b]*n*=44 eyes. VA: Visual acuity.

Table 2 Ophthalmologic findings of the ethambutol optic neuropathy patient with and without visual improvement (follow up 3-12mo)

Parameters	RE (*n*=58)	LE (*n*=58)	OU (*n*=116)
Initial visual acuity (logMAR)	1.15 (0-2.5)	1.3 (0-2.5)	1.3 (0-2.5)
Visual field	*n*=46	*n*=46	*n*=93
Visual field (MD)	-15.3±9.6	-15.5±9.6	-13.4 (-33.6 to -1)
Visual field (PSD)	6.2±2.9	5.8±2.5	5.9±2.7
GCIPL thickness (μm)	*n*=37	*n*=40	*n*=77
Average	76 (54-94)	77 (27-90)	77 (27-94)
Minimum	70 (1-86)	72 (19-87)	71 (1-87)
Superior	76 (50-90)	77 (26-93)	76 (26-93)
Superonasal	77.11±12	74.5±14.6	75.75±13.4
Inferonasal	74.76±13.8	71.18±14.9	72.9±14.4
Inferior	75 (13-104)	74.5 (22-95)	75 (13-104)
Inferotemporal	81 (50-95)	76.5 (23-89)	79 (23-95)
Superotemporal	79 (54-92)	77 (25-92)	78 (25-92)
RNFL thickness (μm)	*n*=46	*n*=46	*n*=93
Average	100.15±22	99.37±17.7	99.87±19.8
Superior	119.57±29.3	125.17±28.9	122.51±28.9
Nasal	70.5 (44-117)	68 (54-102)	70 (44-117)
Inferior	126.41±31.6	125.11±26.5	125.88±28.9
Temporal	79 (33-187)	72.5 (38-112)	75 (33-187)
Pattern ERG	*n*=15	*n*=15	*n*=33
P50 amplitude (μV)	5.2 (3.1-11.4)	4.6 (1.8-8)	4.8±2.2
P50 implicit time (ms)	54.5±5.6	53.6±7.6	53.8±6.5
N95 amplitude (μV)	-6.1±3.4	-5.97±2.8	-5.6±3.5
N95 implicit time (ms)	106.6±9.5	108.1±11.7	104 (47.8-131)
VEP	*n*=19	*n*=19	*n*=42
P2 amplitude (μV)	12.4±5.4	13.2±5.7	11.45 (4.2-26.8)
P2 implicit time (ms)	130 (97.6-165)	128 (102-173)	135.6 (97.6-175)

MD: Mean deviation; PSD: Pattern standard deviation; GCIPL: Ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer; ERG: Electroretinogram; VEP: Visual evoked potentials; RE: Right eye; LE: Left eye; OU: Both eyes.

The incidence of EON increased with higher daily doses, from 0.3% at 15 mg/kg to 3% at 20 mg/kg and 5%-6% at 25 mg/kg, 20 consistent with previous reports[8,11,21,25].

The minimum duration of ethambutol exposure before symptom onset in our study was 2mo, in line with the findings of previous study. The median treatment duration was 9mo,

and the risk of EON was higher with prolonged therapy, increasing from 12% with <2mo of treatment to 51% with 2-6mo and 37% with >6mo[23]. In our study, ethambutol was discontinued in all patients immediately upon diagnosis of EON, regardless of their tuberculosis treatment status. This immediate cessation was implemented as a critical intervention to prevent permanent visual damage, as continuing ethambutol despite visual symptoms could lead to irreversible vision loss[26-27]. After ethambutol discontinuation, all patients were referred back to their treating pulmonologists for modification of their tuberculosis treatment regimen. This approach prioritizes preventing permanent visual disability while ensuring continued appropriate treatment for tuberculosis through alternative drug combinations[28-29].

At presentation, the mean BCVA was 1.3 logMAR (Snellen equivalent 20/400), but some patients with normal acuity had other signs of optic neuropathy, such as visual field defects, dyschromatopsia, or reduced contrast sensitivity. This underscores the importance of comprehensive ophthalmic assessment in patients taking ethambutol, even in the absence of visual acuity loss. Most patients (74.1%) reported gradual, bilateral visual decline, and 72.4% had a normal fundus appearance initially. These findings highlight the need for a detailed history, including medication review, in patients presenting with insidious bilateral visual symptoms and unremarkable optic discs. EON can manifest as early as 15d after starting ethambutol[30] and up to 2y later[5,24], emphasizing the importance of vigilance throughout the course of treatment. Visual field testing revealed generalized depression (52.4%), central scotoma (26.2%), and hemianopia (12.6%), consistent with prior reports[31]. Bitemporal hemianopia, though uncommon, has been described in EON, with chiasmal and optic tract involvement demonstrated on magnetic resonance imaging[32-33]. OCT studies have shown increased peripapillary RNFL thickness at 6mo[34] and decreased macular GC-IPL thickness as an early sign of toxicity[35]. Pattern VEP may detect subclinical EON, with prolonged P100 latency preceding visual function changes[13]. While electrophysiology and OCT are valuable for detecting and monitoring EON[6,9,11,16,36-37], they were used in our study primarily to confirm the diagnosis and assess progression, as all patients were symptomatic at presentation.

Color vision assessment, using tests such as Ishihara plates or the Farnsworth D-15 test, is a quick, inexpensive, and widely available method that could be easily incorporated into the routine monitoring of patients receiving ethambutol therapy. Dyschromatopsia, particularly in the red-green axis, is often one of the earliest signs of EON, preceding visual acuity loss and other symptoms[1,22]. By detecting color vision deficits early, primary care providers could promptly refer patients to ophthalmologists for further evaluation and management, potentially preventing severe and irreversible vision loss.

In Indonesia, tuberculosis patients are required to visit primary care clinics monthly to obtain their medications, including ethambutol[38]. This provides an ideal opportunity to implement regular color vision screening as part of the standard monitoring protocol. At each visit, patients could undergo brief color vision testing, which takes only a few minutes to administer and interpret. Any patient demonstrating new or worsening color vision deficits would be referred urgently to an ophthalmologist for a comprehensive examination, including visual acuity, visual fields, OCT, and electrophysiology as indicated.

The implementation of monthly color vision testing in primary care could greatly enhance the early detection of EON by increasing screening frequency, improving access to screening, enhancing patient awareness and education, facilitating timely referral and intervention, and potentially reducing healthcare costs associated with advanced disease. To successfully implement this approach in Indonesia, primary care providers would need to be trained in color vision testing, clinics would need to be equipped with appropriate testing materials, clear referral pathways would need to be established, and patients would need to be educated about the importance of regular screening and symptom reporting. Further research is needed to validate the effectiveness and cost-effectiveness of monthly color vision screening in improving EON detection and outcomes in the Indonesian context[39-41].

Visual recovery occurred in 56.9% of our patients after stopping ethambutol, similar to the 50% improvement rate reported by Chen *et al*[11] at >6mo and Tsai and Lee[10] at 1-3y. However, other studies have found lower rates of recovery, ranging from 31%[5] to 42.2%[38]. This variability raises the question of whether specific demographic or clinical factors influence visual outcomes in EON.

Although several risk factors for developing EON have been identified, including older age, hypertension[28,42], renal impairment[11], higher ethambutol dose[5], longer treatment duration[34,42-45], and smoking[42], the prognostic factors for visual recovery remain poorly defined[5,11,46]. Previous studies found no significant association between visual improvement and daily or cumulative ethambutol dose, treatment duration, or glomerular filtration rate[11]. While not statistically significant, it was observed trends toward older age, higher ethambutol dose, and lower body weight in patients without visual recovery[28].

In contrast to previous studies, we found significant differences in age, ethambutol duration and daily dose, hypertension, and kidney disease between patients with and without visual improvement. Younger age, lower dose and shorter course of ethambutol, better presenting BCVA, and absence of hypertension or renal disease were predictive of visual

recovery[5,7,11,42]. These findings are supported by Srithawatpong *et al*[41] who identified female sex and better initial BCVA as significant predictors of visual improvement.

Our study's larger sample size (51 patients), with 56.9% showing visual recovery, compared to previous reports may have allowed us to detect these significant prognostic factors[5,7,11,42]. Additionally, the visual recovery group had significantly better presenting BCVA than the non-recovery group (1.15 *vs* 1.4 logMAR), and there was a positive correlation between initial and final BCVA. This aligns with the results of Srithawatpong *et al*[41] and Ambika *et al*[19], who found that worse initial BCVA (>1.0 logMAR or <20/200) was associated with poor visual outcomes.

Notably, all patients with kidney disease in the non-recovery group also had hypertension, highlighting the importance of close monitoring and dose adjustment in this high-risk population. Ethambutol is primarily eliminated by the kidneys, and renal dysfunction can lead to drug accumulation and increased toxicity risk. As renal function declines with age, older patients may be particularly vulnerable to EON[23].

The presence of optic atrophy at presentation was another poor prognostic sign in our study, consistent with the findings of previous studies[7,11,42]. None of the patients with optic disc pallor at baseline demonstrated visual improvement.

Interestingly, we found no difference in the prevalence of diabetes between the recovery and non-recovery groups, similar to previous studies[11,38]. In fact, Chen *et al*[28] observed a reduced risk of EON in patients with diabetes after adjusting for age, sex, hypertension, and renal disease, suggesting a potential protective effect that warrants further investigation.

Our study has several limitations, including its single-center, retrospective design and lack of standardized color vision testing and renal function data. Future prospective, multicenter studies with comprehensive visual function assessment, OCT and electrophysiology, and baseline nutritional and renal parameters could provide further insights into the predictors of visual recovery in EON. Survival analysis exploring the time course of visual improvement from ethambutol discontinuation would also be valuable. In conclusion, this study identified younger age, lower ethambutol dose and shorter treatment duration, better presenting BCVA, and absence of hypertension or renal impairment as significant predictors of visual recovery in EON. The presence of optic atrophy at diagnosis was associated with poor visual outcomes. These findings can help guide medication dosing, monitoring, and patient counselling in the management of this potentially devastating complication of tuberculosis treatment. Additionally, the incorporation of regular color vision testing into the routine monthly monitoring of tuberculosis patients in primary care settings in Indonesia could significantly improve the early detection and management of EON, ultimately reducing the incidence of severe and permanent visual impairment associated with this condition.

In conclusion, 58 EON patients at a tertiary eye center (2017-2022) in Indonesia, demographics, ethambutol treatment, ophthalmologic findings were collected. Visual outcomes after ethambutol cessation was assessed at 3-12mo. Patients were categorized as having visual improvement (≥2 Snellen lines and/or >5° visual field gain) or no improvement. Younger age, lower ethambutol dose, shorter treatment duration, better presenting visual acuity, and absence of hypertension or renal impairment were significant predictors of visual improvement. The presence of optic atrophy at initial presentation was a poor prognostic sign, with none of the affected patients demonstrating visual recovery.

These findings underscore the importance of close monitoring and dose adjustment in high-risk populations, particularly older patients and those with hypertension or kidney disease. Early detection of EON through comprehensive ophthalmic assessment, including color vision testing, visual fields, OCT, and electrophysiology, is crucial for preventing irreversible vision loss. The incorporation of regular color vision screening into routine tuberculosis treatment monitoring in primary care settings could significantly improve the early identification and management of EON in Indonesia, where tuberculosis burden is high and access to specialized ophthalmic care may be limited.

Implementing a standardized protocol for monthly color vision testing during tuberculosis treatment visits, along with clear referral pathways to ophthalmologists for patients with suspected EON, could greatly enhance the detection and management of this potentially devastating complication. By catching EON early and promptly intervening with medication adjustments and close follow-up, the incidence of severe and permanent visual impairment could be reduced, ultimately improving the quality of life for patients undergoing tuberculosis treatment.

Future prospective, multicenter studies with comprehensive visual function assessment, OCT, electrophysiology, and baseline nutritional and renal parameters could provide further insights into the predictors of visual recovery in EON. Additionally, research evaluating the feasibility, acceptability, and cost-effectiveness of integrating color vision screening into tuberculosis treatment monitoring in primary care settings in Indonesia would be valuable for informing the design and implementation of practical, sustainable interventions to improve EON outcomes in resource-limited settings.

In conclusion, this study contributes to our understanding of the clinical features, risk factors, and prognostic indicators in EON, emphasizing the importance of early detection and

intervention in preventing permanent vision loss. The potential role of color vision testing in primary care settings as a simple, low-cost tool for improving EON detection and management in Indonesia warrants further investigation and could serve as a model for other high-tuberculosis-burden countries facing similar challenges in preventing this serious treatment complication.

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