The prevalence, risk factors and outcomes of retinopathy of prematurity at a tertiary care centre in South Africa

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Background. Retinopathy of prematurity (ROP) is a significant cause of preventable blindness in premature infants. The prevalence of ROP is increasing, particularly in resource-constrained settings. Low birthweight (BW), low gestational age (GA) and other neonatal risk factors are identified as key contributors. In South Africa (SA), intravitreal bevacizumab (IVB) is commonly used for treating type 1 ROP due to its accessibility and cost-effectiveness.
Objectives. To evaluate the prevalence, risk factors and outcomes of ROP in a tertiary hospital in SA infants, with a focus on the use of IVB for type 1 ROP.
Methods. This retrospective file audit, conducted at Rob Ferreira Hospital, reviewed ROP referrals from January 2020 to December 2023. Infants were screened by a specialist ophthalmologist, and treatment with IVB was administered to those diagnosed with type 1 ROP according to the Early Treatment for Retinopathy of Prematurity study protocol. Follow-up was conducted until full vascularisation, or 60 weeks post menstrual age for the respective groups.
Results. A total of 267 infants were referred, with an ROP prevalence of 27.0%. Type 1 and type 2 ROP accounted for 31.9% and 68.1% of diagnoses, respectively. Of screened infants, 8.6% (*n*=23/267) required treatment with IVB, with no reported complications. Of the 72 infants diagnosed with any ROP, 40.3% did not return for follow-up until discharge was indicated.
Conclusion. This study highlights a similar ROP prevalence rate to other SA studies, but yields a markedly higher ROP treatment rate. IVB proved to be a safe and effective treatment option, with no observed complications. However, a 40.3% attrition rate underscores the need for strengthened follow-up systems and improved care pathways. Addressing follow-up challenges and exploring alternative treatment modalities, such as laser photocoagulation, may help to improve long-term outcomes for at-risk infants.

Keywords: retinopathy of prematurity, preterm infants, intravitreal bevacizumab, low birthweight, resource-limited settings, neonatal screening, treatment outcomes, South Africa

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Retinopathy of prematurity (ROP) is a significant cause of preventable blindness in infants.[1] This retinal vaso-proliferative disease arises from multifactorial aetiology, with lower gestational age (GA), low birthweight (LBW) and hyperoxia being the most frequently identified risk factors.[2] Additionally, hyperglycaemia, slower postnatal growth, neonatal infections (especially fungal) and genetic factors have been implicated in increasing the risk of ROP.[3] The classification of ROP is standardised by the International Classification of ROP (ICROP3), revised in 2021, which facilitates appropriate and timely treatment (Fig. 1).[4]

In recent years, advancements in neonatal care have markedly improved the survival rates of LBW infants, leading to a corresponding rise in ROP prevalence.[5] Globally, it is estimated that 50 000 infants are diagnosed with ROP annually.[6] South African (SA) data suggest that 16 000 infants annually are at risk of developing ROP.[7,8] In SA, ROP accounts for 10.6 - 13.8% of attendees in schools for the blind.[9,10] Improved management of ROP can improve the morbidity of our affected populations.

A review of the literature indicates that the prevalence of ROP in Africa varies widely. A 2018 retrospective review in Kenya found that 41.7% of 103 premature infants screened were diagnosed with ROP.[11] While a 2015 study in Nigeria reported a prevalence of 15% among 80 examined infants.[12] In 2016, Visser Kift *et al.*[13] determined the SA prevalence of ROP among infants at Tygerberg Hospital to be 33.4% (*n*=1 104). Two recent SA studies also estimate the prevalence at 27.6% (*n*=135)[14] and 24.5% (*n*=94).[15] More prevalence data in the SA context will assist in the creation of more representative guidelines. This will facilitate better patient management, and allow us to better understand the variance in ROP data.

Bevacizumab, a monoclonal anti-vascular endothelial growth factor (VEGF), is a rapidly growing treatment modality for ROP in the SA context due to its lower cost and ease of use.[16] This is because bevacizumab does not require a general anaesthetic, and therefore no neonatal anaesthetists, nor resource-intensive monitoring after anaesthesia. Intravitreal bevacizumab (IVB) can be done with topical anaesthesia, has been shown to be 95% efficient in patients with 'threshold disease' and is more effective in treating posterior zone disease than conventional laser photocoagulation.[16,17] In many resource-constrained settings such as SA, off-label use of IVB is the only treatment modality available to ophthalmologists to manage ROP.

As with photocoagulation, anti-VEGFs do not come without risks. The safety profile and pharmacokinetics of this drug in neonates is not completely understood.[18] There are serious adverse reactions possible with IVB: concerns about systemic effects, ROP recurrence, endophthalmitis, iatrogenic cataract and accelerated retinal detachment.[17] The literature regarding the off-label use of

IVB for ROP is increasing quickly.[18] Nonetheless, many of these studies consist of retrospective case series or reports, with only a limited number offering robust evidence.[18] It is therefore important to better understand the outcome and complications of IVB in the SA setting.

Methods

This was a retrospective study conducted at the Department of Ophthalmology, Rob Ferreira Hospital, SA. The unit is in a tertiary referral centre in Mpumalanga Province, hosting ~369 beds.[19] The investigators reviewed all the ROP referrals made to the department between January 2020 and December 2023. Referrals are received from within the hospital as well as from nearby hospitals when an infant is <32 weeks GA, born with a birthweight <1 500 g, or born with a birthweight >1 500 g and with significant risk factors (sepsis, supplemental oxygen, intraventricular haemorrhage (IVH), anaemia, blood transfusions, organisms on blood culture.)

ROP screening was performed by the same specialist ophthalmologist throughout the study period. Screening was performed in aseptic conditions, using an indirect binocular ophthalmoscope with a condensing lens. Patients determined to have type 1 ROP, according to early treatment of retinopathy of prematurity treatment protocol (Table 1),[20] were treated with IVB within 72 hours.[21] Patients with type 2 ROP were followed up until fully vascularised, and patients with type 1 ROP were followed up until 60 weeks post menstrual age.[21]

All patients' notes were made in duplicate and kept on record in the department. A central register was used to record all screened patients. These records were used to collect and compile the data in the study. All patients seen by the screening team had their appointments documented and recorded on the register. A clear follow-up plan or final outcome was recorded for every patient.

Results

A total of 267 infants were referred to the ophthalmology department over a 3-year period between January 2020 and December 2023. The screening yielded 72 patients with ROP, demonstrating a prevalence of 27.0% (95% confidence interval (CI) 22.0 - 32.6) of all referred patients (Table 2). Of the 72 patients with ROP, type 1 and type 2 ROP accounted for 31.9% (*n*=23) and 68.1% (*n*=49), respectively. One infant died in the study period. All remaining infants were discharged or lost to follow-up.

The mean (standard deviation (SD)) birthweight of screened infants was 1 350.0 (276.2) g, and the mean (SD) GA was 30.3 (2.4). The data show that the cohort with the lowest GA (24 - 26 weeks) and lowest birthweight (800 - 999 g) had the highest prevalence of ROP: 57.1% (*n*=8/14) and 73.7% (*n*=14/19), respectively (Table 2).

All 267 referral documents reviewed contained at least one identified risk factor, as shown in Fig. 2. Among the patient groups, those with IVH (*n*=8) exhibited the highest prevalence of ROP at 37.5% (*n*=3), although this group had a notably small sample size. ROP rates exceeded 30% in infants with GA ≤32 weeks (30.7%), LBW (≤1 500 g) (30.3%) and sepsis (31.5%). Additionally, significant prevalence rates of ROP were observed in infants requiring oxygen therapy (30.4%) and those who received ≥1 blood transfusion (30.6%).

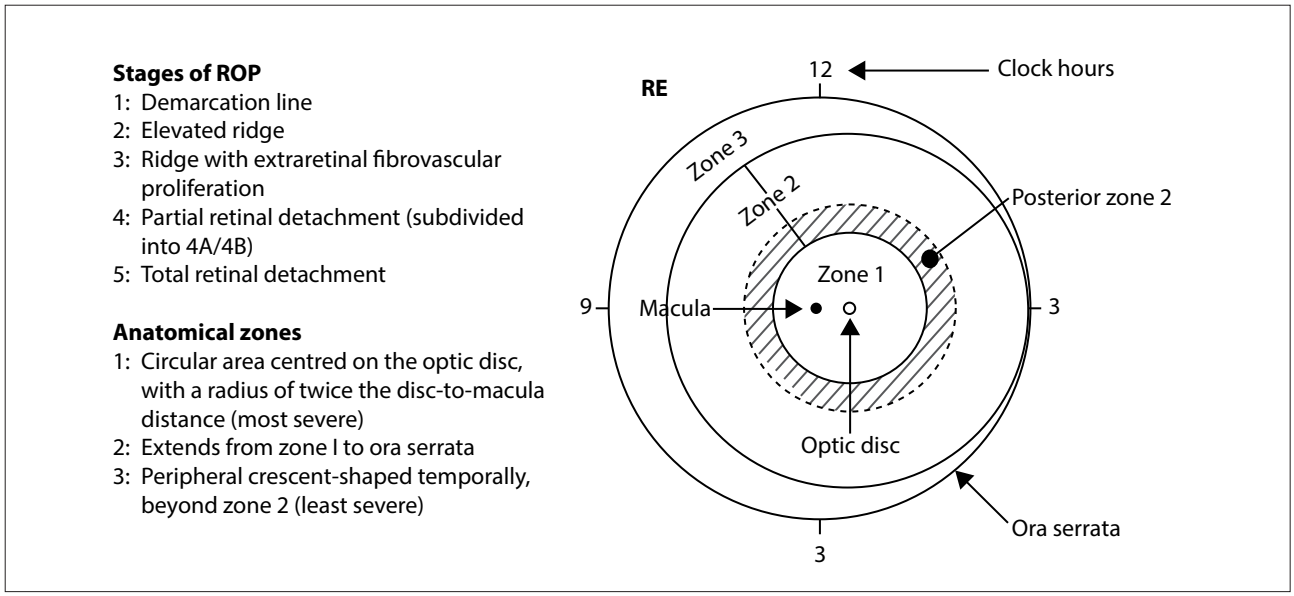

Fig. 1. International Classification of Retinopathy of Prematurity.[4] (ROP = retinopathy of prematurity.)

Table 1. Revised indications for the early treatment of retinopathy of prematurity

Zone/plus* disease	Stage 1	Stage 2	Stage 3
Zone 1			Type 1
Zone 1 and plus	Type 1	Type 1	Type 1
Zone 2			
Zone 2 and plus		Type 1	Type 1
Zone 3			
Zone 3 and plus			

Type 1 highlighted blocks indicate infants who are to be treated within 72 hours. Blank blocks indicate infants classified as type 2 retinopathy of prematurity (ROP), who should be observed.[20]
*Plus disease is a severe form of ROP where retinal blood vessels become abnormally enlarged and twisted.

There were 23 infants who were treated with IVB after being classified as type 1 ROP (Table 3). No cases of endophthalmitis, vitreous haemorrhage, thromboembolic events or death occurred in the treatment group. One patient had bilateral peripheral tractional retinal detachment (stage 4), but this was noted prior to treatment and was not influenced by the IVB. Of the 23 treated patients, only 56.5% (*n*=13) completed their follow-up examinations until 60 weeks post menstrual age. Of the 10 who did not complete the follow-up course, 5 were noted to be almost fully vascularised before defaulting follow-up. Only 2 patients required >1 IVB, and both were fully vascularised at discharge. Among all 72 patients diagnosed with ROP, only 59.7% (*n*=43) followed up until discharge was indicated. Of the 29 remaining patients, 1 died in the neonatal intensive care unit (NICU), and the remaining 28 did not attend all their follow-up appointments.

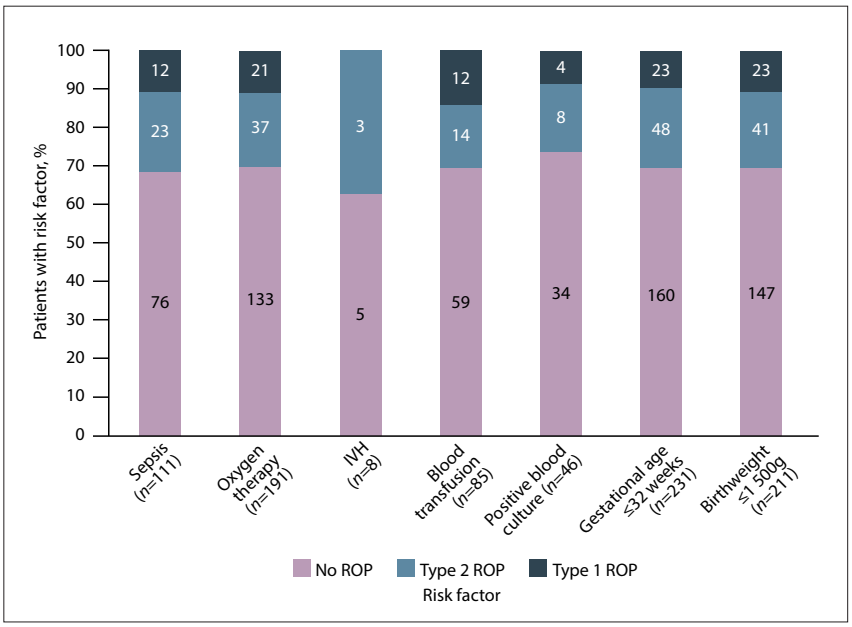

Fig. 2. Risk factors in the study population who were screened for retinopathy of prematurity (N=*267). (ROP = retinopathy of prematurity; IVH = intraventricular haemorrhage.)*

Discussion

This review set out to describe/assess the prevalence and risk factors associated with ROP in an SA setting. The result in this study closely mimics previous studies conducted within SA: a 2016 cross-sectional study conducted at Tygerberg Hospital showed a ROP rate of 33.4% (*n*=1 104),[13] compared with our study's 27.0% (*n*=267). This again is similar to two reported studies from Kalafong Hospital (24.5%, *n*=94)[15] and Groote Schuur Hospital (29.6%, *n*=135).[14]

Our data confirm that LBW and low GA remain the strongest predictors of ROP. Although a limited number of IVH infants

Table 2. Numbers and proportions of screened infants developing ROP according to GA and birthweight (*N*=267)

Characteristic	Total, *n*	No ROP, *n* %	Any ROP, *n* %	Type 1, *n* %	Type 2, *n* %
GA, weeks (mean (SD))					
24 - 26 (25.7 (0.6))	14	6 (42.9)	8 (57.1)	4 (28.6)	4 (28.6)
27 - 29 (28.3 (0.7))	79	48 (60.8)	31 (39.2)	9 (11.4)	22 (27.8)
30 - 32 (30.9 (0.9))	138	106 (76.8)	32 (23.2)	10 (7.2)	22 (15.9)
33 - 35 (33.6 (0.6))	29	28 (96.3)	1 (3.4)	0 (0)	1 (3.4)
≥36 (37.1 (1.1))	7	7 (100)	0 (0)	0 (0)	0 (0)
Total (30.3 (2.4))	267	195 (73.0)	72 (27.0)	23 (8.6)	49 (18.4)
Birthweight, g (mean (SD))					
800 - 999 (916.7 (57.6))	19	5 (26.3)	14 (73.7)	8 (42.1)	6 (31.6)
1 000 - 1 199 (1102.7 (51.8))	49	29 (59.2)	20 (40.8)	8 (16.3)	12 (24.5)
1 200 - 1 399 (1 282.2 (63.1))	96	72 (75.0)	24 (25.0)	4 (4.2)	20 (20.8)
1 400 - 1 599 (1 482.3 (57.8))	68	60 (88.2)	8 (11.8)	2 (2.9)	6 (8.8)
≥1 600 (1 860.5 (253.5))	35	29 (82.9)	6 (17.1)	0 (0)	6 (17.1)
Total (1 350.0 (276.2))	267	195 (73.0)	72 (27.0)	23 (8.6)	49 (18.4)

ROP = retinopathy of prematurity; GA = gestational age.

Table 3. Outcomes and complications of patients with type 1 ROP treated with bevacizumab (*N*=23)

			Outcome	
Zone	*n*	Complications, *n*	Fully vascularised/discharged, *n* (%)	Lost to follow-up, *n* (%)
Zone 1	8	0	5 (62.5)	3 (37.5)
Zone 2	11	0	6 (54.5)	5 (45.5)
APROP	2	0	1 (50.0)	1 (50.0)
Not noted	2	0	1 (50.0)	1 (50.0)
Total	23	0	13 (56.5)	10 (43.5)

ROP = retinopathy of prematurity; APROP = aggressive posterior ROP.
Type 1 ROP infants had to be followed up until 60 weeks post menstrual age, and type 2 ROP infants had to be followed up until fully vascularised. Any patients who did not fulfil these criteria were deemed lost to follow-up.

(*n*=8) were included, their 37.5% ROP prevalence was comparable with infants ≤29 weeks GA (41.9%, *n*=39/93) and infants with a birthweight ≤1 399 g (35.4%, *n*=58/164). A consistent indirect relationship between GA/birthweight and ROP was demonstrated across the different GA/LBW cohorts. Our study suggests that in resource-constrained settings, there are certain extremely high-risk groups that warrant prioritised and monitored screening. These are infants who show very high rates of ROP requiring intervention, such as LBW infants <1 200 g and infants with a GA <30 weeks. These two cohorts show treatment rates of 23.5% (*n*=16/68) and 14.0% (*n*=13/93), respectively. Approximately one in every five infants screened in these two aforementioned high-risk cohorts will require sight-saving intervention.

In our study of 267 infants, all of our included risk factors carried similar weights. From Fig. 2, we can see that each of the screening criteria/risk factors have a relatively equal prevalence of ROP (26.1 - 37.5%). There were few IVH patients, and more numbers are needed to delineate its slightly higher ROP prevalence. No ethnic associations were reported in our data, as this is not part of referral protocols.

Of all screened infants, an ROP treatment rate of 8.6% (*n*=23/267) was demonstrated. This is substantially greater than those in other SA studies, which had a treatment rates of 2.5% (*n*=27/1 104),[13] 1.5% (*n*=2/135)[14] and 1.5% (6/356).[22] The latter two studies had lower screening cut-offs for inclusion (<1 251 g and ≤1 500 g, respectively), and therefore higher-risk populations, while still showing a lower treatment rate. These studies used the same treatment guidelines as our protocol (Table 1). Therefore, we can attribute the increased treatment rate to our specific population and not a change in management strategies. Visser Kift *et al.*[13] and Keraan *et al.*[14] demonstrated that no infants with type 1 ROP were observed above their respective weight thresholds of <1 000 g and <1 250 g. In contrast, our data revealed that 6 infants exceeded the 1 250 g screening threshold, and 15 infants exceeded the 1 000 g threshold. These accounted for 26.1% (*n*=6/23) and 65.2% (*n*=15/23) of our treatment group, respectively.

No cases of ROP recurrence, endophthalmitis, iatrogenic cataract or accelerated retinal detachment associated with IVB administration were observed in our treatment group, which demonstrated favourable outcomes. These findings underscore the safety and efficacy of IVB in our clinical setting. Our higher treatment rate compared with other local studies warrants careful examination. Two possible theories could explain this discrepancy, although the exact reasons remain unclear and merit further investigation. Firstly, a screening bias might be at play. It is possible that our specialist ophthalmologist adopts a more cautious approach, opting to overtreat borderline cases of type 1 ROP rather than risk undertreatment. Secondly, challenges within our NICU, such as poor oxygen saturation monitoring, high infection rates and other suboptimal neonatal care practices may contribute to a higher incidence of type 1 ROP. Notably, our prevalence data align closely with that of other SA studies, suggesting that we are not dealing with a higher-risk population overall. Future studies should explore these potential factors in greater depth to understand the observed differences in treatment rates.

The attrition rate among our 72 infants with ROP was 40.3% (*n*=29/72), which is markedly higher than the 8.9% and 13.8% reported in two other SA studies.[14,22] This concerning statistic is particularly significant in our setting, where IVB is the only available treatment modality. Unlike conventional laser photocoagulation, IVB necessitates more frequent and prolonged follow-up, posing a substantial challenge for populations with limited access to healthcare facilities, particularly in less urbanised regions. This underscores the potential benefits of laser therapy in settings where reliable follow-up is less feasible. Additionally, extraordinary care must be taken to ensure thorough screening of LBW and low GA infants, with senior clinicians establishing robust safety protocols to prevent these vulnerable patients from being missed. While IVB remains a safe and effective treatment, laser therapy could offer a strategic advantage in certain contexts, though its broader implementation is hindered by the significant resource demands required to sustain it in smaller, resource-limited centres. Further research is needed to identify and address the specific barriers to follow-up care in rural and underserved populations, including logistical, socioeconomic and healthcare system-related factors.

A key limitation of this study is that it does not fully represent all infants born at Rob Ferreira Hospital and its catchment area, as some infants were likely missed. While most infants are referred to the ophthalmology department for screening, a proportion are discharged from the nursery before ROP screening is conducted. They are also not provided with a follow-up screening appointment at the eye clinic. However, the number of infants affected by this gap in care is relatively small. Efforts to ensure systematic tracking and scheduling of follow-up appointments for all at-risk infants could help to address this limitation in future studies.

Conclusion

This study highlights the burden of ROP in an SA tertiary referral centre, with a prevalence of 27.0%, aligning with rates from similar local studies. The treatment rate of 8.6% was higher than those reported in other SA centres, potentially reflecting differences in neonatal care. IVB proved to be a safe and effective treatment option, with no treatment-related complications observed. However, the attrition rate of 40.3% underscores the need for improved follow-up systems, particularly in rural and underserved populations. Enhanced referral pathways, stronger oversight from senior clinicians and the exploration of alternative treatment modalities, such as laser photocoagulation, may help to address these challenges. Further research is required to investigate the underlying causes of higher treatment rates, and to develop strategies for improving follow-up adherence and access to care.

Data availability. All raw data generated during this study will be made available by the corresponding author upon reasonable request.

Declaration. None.

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Author contributions. DCG: conceptualisation, data collection, formal analysis, statistics, manuscript writing and project administration. SJB: supervision, manuscript review and editing, and validation. BB: data curation.

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1. Bedrossian RH, Carmichael P, Ritter J. Retinopathy of prematurity (retrolental fibroplasia) and oxygen. Clinical study. II. Further observations on the disease. Am J Ophthalmol 1954;37(1):78-86. https://doi.org/10.1016/0002-9394(54)92034-6
2. Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. Lancet 2013;382(9902):1445-1457. https://doi.org/10.1016/s0140-6736(13)60178-6
3. Kim SJ, Port AD, Swan R. Retinopathy of prematurity: A review of risk factors and their clinical significance. Surv Ophthalmol 2018;63(5):618-637. https://doi.org/10.1016/j.survophthal.2018.04.002
4. Chiang MF, Quinn GE, Fielder AR, et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology 2021;128(10):e51-e68. https://doi.org/10.1016/j.ophtha.2021.05.031

5. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. N Engl J Med 2012;367(26):2515-2526. https://doi.org/10.1056/nejmra1208129
6. Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 2008;84(2):77-82. https://doi.org/10.1016/j.earlhumdev.2007.11.009
7. Visser L, Singh R, Young M, Lewis H, McKerrow N. Guideline for the prevention, screening and treatment of retinopathy of prematurity in South Africa. S Afr Med J 2017;107(3):215-218. https://doi.org/10.7196/samj.6305
8. Varughese S, Gilbert C, Pieper C, Cook C. Retinopathy of prematurity in South Africa: An assessment of needs, resources and requirements for screening programmes. Br J Ophthalmol 2008;92(7):879-882. https://doi.org/10.1136/bjo.2008.137588
9. O'Sullivan J, Gilbert C, Foster A. The causes of childhood blindness in South Africa. S Afr Med J 1997;87(12):1691-1695. https://pubmed.ncbi.nlm.nih.gov/9497836/ (accessed 7 May 2025).
10. Esra N, Mayet I. The causes of visual impairment in children in a school for the blind in Johannesburg. SA Ophthalmol J 2020;15(1):26-29. https://jhbeye.com/wp-content/uploads/2020/10/Childhood-blindness-in-South-Africa.pdf (accessed 7 May 2025).
11. Onyango O, Sitati S, Amolo L, et al. Retinopathy of prematurity in Kenya: Prevalence and risk factors in a hospital with advanced neonatal care. Pan Afr Med J 2018;29:152. https://doi.org/10.11604/pamj.2018.29.152.14046
12. Fajolu IB, Rotimi-Samuel A, Aribaba OT, et al. Retinopathy of prematurity and associated factors in Lagos, Nigeria. Paediatr Int Child Health 2015;35(4):324-328. https://doi.org/10.1080/20469047.2015.1109277
13. Visser Kift E, Freeman N, Cook C, et al. Retinopathy of prematurity screening criteria and workload implications at Tygerberg Children's Hospital, South Africa: A cross-sectional study. S Afr Med J 2016;106(6):602-606. https://doi.org/10.7196/SAMJ.2016.v106i6.10358
14. Keraan Q, Tinley C, Horn A, Pollock T, Steffen J, Joolay Y. Retinopathy of prematurity in a cohort of neonates at Groote Schuur Hospital, Cape Town, South Africa. S Afr Med J 2017;107(1):64-69. https://doi.org/10.7196/samj.2016.v107.i1.11226
15. Delport SD, Swanepoel JC, Odendaal PJ, et al. Incidence of retinopathy of prematurity in very-low-birth-weight infants born at Kalafong Hospital, Pretoria. S Afr Med J 2002;92(12):986-990. https://pubmed.ncbi.nlm.nih.gov/12561416/ (accessed 7 May 2025).
16. Kana H, Mayet I, Soma D, Dawood Alli H, Biddulph S. The efficacy of intravitreal antivascular endothelial growth factor as primary treatment of retinopathy of prematurity: Experience from a tertiary hospital. S Afr Med J 2017;107(3):215-218. https://doi.org/10.7196/SAMJ.2017.v107i3.11080
17. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;364(7):603-615. https://doi.org/10.1056/NEJMoa1007374
18. Hapsari D, Sitorus RS. Intravitreal bevacizumab in retinopathy of prematurity. Asia Pac J Ophthalmol 2014;3(6):368-378. https://doi.org/10.1097/APO.0000000000000039
19. Parliamentary Monitoring Group. STC160303: Report of the Portfolio Committee on Health on Oversight visit to Mpumalanga province from 22 to 23 September 2014, dated 24 February 2016. Parliamentary Monitoring Group, 2016. https://pmg.org.za/tabled-committee-report/2660/#:~:text=The%20hospital%20has%20a%20total,of%20stay%20of%207.3%20days (accessed 22 October 2024).
20. Good WV, Hardy RJ, Dobson V, et al. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomised trial. Arch Ophthalmol 2003;121(12):1684-1694. https://doi.org/10.1001/archopht.121.12.1684
21. Fierson WM. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2018;142(6):e20183061. https://doi.org/10.1542/peds.2018-3061
22. Van der Merwe SK, Freeman N, Bekker A, Harvey J, Smith J. Prevalence of and risk factors for retinopathy of prematurity in a cohort of preterm infants treated exclusively with non-invasive ventilation in the first week after birth. S Afr Med J 2013;103(2):96. https://doi.org/10.7196/samj.6131

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