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Cost-effectiveness of bevacizumab versus ranibizumab for treatment-requiring retinopathy of prematurity: a multicenter real-world cohort study

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Abstract

Background

Retinopathy of prematurity (ROP) is a leading cause of preventable childhood blindness that requires timely treatment and prolonged specialist follow-up. Although bevacizumab and ranibizumab are widely used as first-line intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies for treatment-requiring ROP, comparative real-world economic evidence remains limited. This study evaluated the clinical outcomes, healthcare utilization, and cost-effectiveness of bevacizumab versus ranibizumab within a multicenter neonatal referral network in Colombia.

Methods

This multicenter retrospective cohort study included preterm infants with treatment-requiring ROP managed with first-line intravitreal bevacizumab or ranibizumab across 14 healthcare institutions between 2012 and 2023. Clinical follow-up extended through 60 weeks postmenstrual age. The outcomes included retreatment, healthcare utilization, quality-adjusted life-years (QALYs), and direct medical costs from the Colombian healthcare system perspective. Deterministic and probabilistic cost-effectiveness analyses comprising 100,000 Monte Carlo simulations were performed using incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB) at a willingness-to-pay threshold of USD 5,180.80 per QALY.

Results

A total of 121 infants were included, of whom 47 received bevacizumab and 74 received ranibizumab. Retreatment occurred significantly less frequently after bevacizumab than after ranibizumab (6.38% vs. 48.65%; $p < 0.0001$). The mean ROP-related costs were substantially lower for bevacizumab (USD 1,706.10 ± 375.64 vs. USD 2,681.88 ± 750.01; $p < 0.0001$), whereas the QALYs were comparable between groups (0.39 ± 0.05 vs. 0.38 ± 0.07; $p = 0.1828$). Deterministic analysis demonstrated the economic dominance of bevacizumab. Probabilistic sensitivity analysis revealed an 86.55% probability that bevacizumab was the most cost-effective strategy at Colombia's willingness-to-pay threshold, with a consistently positive NMB across the evaluated willingness-to-pay range. These findings remained consistent across the clinically relevant gestational age, birth weight, and early-stage prophylaxis subgroups.

Conclusions

Bevacizumab was associated with substantially lower retreatment burden, lower healthcare utilization, and reduced direct medical costs without measurable short-term reductions in health-related quality of

life. These findings suggest that bevacizumab represents a high-value first-line anti-VEGF strategy for treatment-requiring ROP and may support evidence-informed resource allocation, reimbursement, and health technology assessment, particularly in resource-constrained healthcare systems.

1. Introduction

Retinopathy of prematurity (ROP) remains a leading yet preventable cause of childhood blindness worldwide and is an increasingly important consequence of improved survival among extremely premature infants [1]. Although advances in neonatal intensive care have increased survival, the availability of specialized ophthalmologic services has not increased uniformly, creating persistent gaps in screening, treatment, and longitudinal follow-up [2–4]. Consequently, unfavorable visual outcomes are increasingly driven by failures in healthcare delivery rather than by the absence of effective therapeutic options [5].

Treatment-requiring ROP can progress rapidly to retinal detachment and irreversible visual impairment if intervention is delayed. While laser photocoagulation remains an established treatment, intravitreal anti–vascular endothelial growth factor (VEGF) therapy has transformed the management of posterior and aggressive disease by promoting rapid regression of pathological neovascularization while preserving the peripheral retina. As a result, anti-VEGF therapy has become a cornerstone of contemporary ROP management [6–11].

Bevacizumab and ranibizumab are the most widely used anti-VEGF agents, yet important differences remain regarding durability, retreatment burden, surveillance requirements, systemic exposure, and acquisition costs. Bevacizumab generally provides longer intraocular VEGF suppression and is frequently associated with lower recurrence rates, whereas ranibizumab has a shorter systemic half-life and has received regulatory approval for ROP in several jurisdictions because of concerns regarding systemic VEGF suppression in premature infants. This therapeutic trade-off has generated ongoing debate regarding the optimal balance between durability, safety, healthcare utilization, and cost [6–11].

The implications of anti-VEGF selection extend beyond pharmacologic efficacy. In neonatal referral networks, where continuity of follow-up may be difficult to maintain, differences in treatment durability can influence retreatment frequency, specialist workload, healthcare utilization, and the risk of delayed recognition of disease reactivation [12, 13]. These considerations are particularly relevant in settings with limited pediatric retinal expertise, where repeated examinations and retreatments may place substantial demands on already constrained services [4, 14, 15]. Furthermore, the marked difference in acquisition cost between bevacizumab and ranibizumab amplifies the potential consequences of treatment selection at both the institutional and health-system levels [1, 16–18].

Despite the expanding use of anti-VEGF therapy, evidence concerning the economic consequences of agent selection remains limited [19–21]. Existing pharmacoeconomic studies have largely focused on adult retinal diseases and cannot be readily extrapolated to premature infants, whose care is characterized by unique physiologic vulnerabilities, prolonged surveillance requirements, caregiver

dependence, and distinct patterns of healthcare utilization [21–24]. These challenges are especially relevant in low- and middle-income settings, where workforce shortages, geographic barriers, and fragmented referral pathways frequently complicate access to specialized care [13].

As anti-VEGF therapy becomes an established component of neonatal retinal care, clinicians, healthcare systems, and policymakers face important decisions regarding medication selection and resource allocation. However, comparative evidence evaluating not only clinical outcomes but also healthcare utilization and economic consequences remains limited. Few real-world investigations have simultaneously examined these dimensions among anti-VEGF agents used for treatment-requiring ROP.

Accordingly, this study evaluated the real-world clinical and economic outcomes of bevacizumab versus ranibizumab as first-line intravitreal monotherapy for treatment-requiring ROP within a multicenter neonatal referral network in Colombia. Retreatment burden, healthcare utilization, quality-adjusted life-years (QALYs), and direct medical costs were assessed to generate evidence capable of informing therapeutic selection, service delivery, resource-allocation decisions in neonatal retinal care, and future randomized controlled trials.

2. Methods

2.1. Study design and settings

This multicenter retrospective cohort study evaluated the clinical and economic outcomes of preterm infants with treatment-requiring ROP who received intravitreal anti–VEGF monotherapy between November 2012 and April 2023 across 14 healthcare institutions in Colombia. The participating centers were accredited by the Colombian Ministry of Health and Social Protection. They were located in the departments of Córdoba and Antioquia, serving predominantly rural, suburban, and low-income urban populations.

Clinical care was provided by a single retina specialist with more than 10 years of experience in ROP management, who served as a consultant across the participating institutions. Screening, treatment decisions, intravitreal administration, and longitudinal monitoring were conducted in accordance with standardized diagnostic and management protocols throughout the study period.

Ethical approval

2.2. **and considerations**

The study was conducted by microscopIA, an institution recognized by the Colombian Ministry of Science, Technology, and Innovation (Call 984, 2021). Ethical approval was obtained from the microscopIA Institutional Review Board (Approval OPH-001). All clinical procedures were performed with written informed consent from parents or legal guardians and in accordance with the Declaration of Helsinki and institutional requirements. Because the study involved retrospective analysis of deidentified

data, additional consent for data use or publication was not required under applicable institutional policies and national regulations.

2.3. Data sources and management

Data were obtained from institutional electronic medical records and a centralized longitudinal database maintained by the attending retina specialist using a prespecified abstraction protocol. Case identification was performed using International Classification of Diseases, Tenth Revision (ICD-10) codes corresponding to treatment-requiring ROP, including H35.14 (stage 3), H35.15 (stage 4), and H35.16 (stage 5). A final data lock was implemented before the statistical analyses.

Trained reviewers performed duplicate extraction of key variables. The extracted information included disease stage, treatment characteristics, retreatment status, follow-up duration, healthcare utilization, and cost components. Discrepancies were resolved through review of source documentation, including medical records, ophthalmologic notes, and operative reports, with unresolved inconsistencies adjudicated by a senior reviewer.

Variable definitions, measurement units, and admissible ranges were predefined before analysis. Implausible values were verified against source documentation. Missing information prompted reexamination of the original records; records lacking essential variables after source verification were excluded, and no statistical imputation was performed.

All the datasets were deidentified before analysis through the removal of direct identifiers and the masking of indirect identifiers in accordance with institutional data-protection procedures. Access to the final locked dataset was restricted to authorized members of the biostatistics and quality control teams.

2.4. Participants

Eligible participants were preterm infants who were born before 37 weeks of gestation or whose birth weight was less than 2,000 g and who developed treatment-requiring ROP and who received intravitreal anti-VEGF monotherapy with either bevacizumab or ranibizumab as first-line treatment. Cases were identified through routine ROP screening programs conducted according to regional and international recommendations [13, 25–27].

Inclusion requires complete clinical documentation and follow-up through 60 weeks postmenstrual age, corresponding to the period during which retinal vascular maturation and posttreatment reactivation are typically monitored following anti-VEGF therapy [28–30].

The exclusion criteria included prior ROP-directed treatment before the index anti-VEGF administration; congenital or acquired ocular conditions that could interfere with disease assessment; incomplete clinical records; loss to follow-up before 60 weeks postmenstrual age; systemic conditions precluding safe ophthalmologic evaluation or intravitreal treatment; and participation in interventional clinical trials for ROP.

2.5. Assessments and interventions

Retinal examinations were performed using binocular indirect ophthalmoscopy as the primary diagnostic modality. Follow-up intervals were individualized according to disease severity, retinal findings, anticipated follow-up reliability, and healthcare access considerations. Evaluations were generally conducted weekly or biweekly, although longer intervals occasionally occurred because of logistical and administrative constraints. When available, wide-field digital fundus imaging was used to document retinal findings and monitor disease progression.

Infants who progressed to treatment-requiring ROP were scheduled for intervention within 48 hours of diagnosis. Treatment selection was based on the disease zone, vascular activity, anticipated continuity of follow-up, pharmacologic characteristics, and clinical feasibility. Intravitreal anti–VEGF monotherapy was generally preferred for zone I and posterior zone II disease, particularly when rapid regression and preservation of peripheral retinal tissue were prioritized. When reliable posttreatment surveillance could not be ensured, laser photocoagulation was considered an alternative because of the lower risk of unrecognized disease reactivation [13, 31].

For infants receiving anti-VEGF therapy, bevacizumab (0.75 mg) or ranibizumab (0.30 mg) was administered as a single intravitreal injection under sterile conditions using topical anesthesia and standardized aseptic techniques. These dosing regimens were selected based on published pharmacologic and clinical evidence supporting efficacy and safety in treatment-requiring ROP [7, 32–35].

Bevacizumab was generally selected for posterior or aggressive disease phenotypes because of its greater intraocular durability and lower anticipated retreatment burden. Ranibizumab was preferentially used when minimizing systemic VEGF exposure was considered clinically desirable, particularly among medically fragile or extremely premature infants, and when consistent posttreatment surveillance was considered feasible [8, 13, 33, 36].

Posttreatment monitoring included ophthalmologic evaluation within 48 hours after injection, followed by serial examinations every 15–21 days to assess retinal regression, vascular maturation, and disease reactivation. Enhanced surveillance was implemented in infants with persistent neovascular activity or delayed peripheral vascularization. Laser photocoagulation was the preferred retreatment modality following anti-VEGF reactivation because of its established effectiveness and lower likelihood of subsequent recurrence [8, 10, 28, 37].

After retinal stability and vascular maturity were confirmed, infants transitioned to annual ophthalmologic follow-up for monitoring of refractive development and late-onset ocular complications. Because follow-up extended through 60 weeks postmenstrual age, potential reactivation occurring beyond this observation period could not be systematically assessed.

Occasionally, geographic, socioeconomic, and administrative barriers delay screening or treatment. In these situations, institutional coordination mechanisms—including social-work support and collaboration with the Colombian Children and Adolescents Police—were implemented to facilitate transportation, prioritize high-risk infants, and reduce preventable delays in ophthalmologic evaluation and intervention.

2.6. Early-stage prophylaxis

During the study period, topical ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) were incorporated off-label into the routine management of infants with stage 1–2 ROP by the attending retina specialist. This practice was informed by emerging computational, experimental, and clinical evidence suggesting that NSAIDs may modulate inflammatory and angiogenic pathways involved in aberrant retinal vascularization [38–42].

Because some infants subsequently progressed to treatment-requiring disease despite prophylaxis, the cohort provided an opportunity to evaluate whether prior NSAID exposure was associated with differences in outcomes following definitive treatment. Accordingly, prophylaxis status and use of prophylactic agents were recorded as prespecified exposure variables and incorporated into the subgroup analyses.

The contraindications included known or suspected hypersensitivity to NSAIDs, severe neonatal hypertension, active gastrointestinal bleeding, renal or hepatic dysfunction, coagulation abnormalities, and clinically significant ocular surface disease, including epithelial defects, keratitis, or marked surface inflammation [43–45]. In infants considered unsuitable for prophylaxis despite an elevated risk of progression, follow-up intervals were shortened, and surveillance intensified.

Before January 2019, early-stage ROP was managed conservatively without pharmacologic prophylaxis. Between January 2019 and June 2020, ketorolac 0.45% was used as the standard prophylactic agent. Beginning in July 2020, nepafenac 0.10% replaced ketorolac due to regional drug shortages and nepafenac's superior retinal penetration [41, 46–48].

Dosing frequency was stratified according to disease severity. Ketorolac was generally administered as one drop per eye every 12 hours for stage 1 disease and every 8 hours for stage 2 disease, whereas nepafenac was administered every 8 hours and every 6 hours, respectively [49–53]. After receiving standardized instructions regarding administration procedures, storage conditions, and adverse event monitoring, caregivers administered treatment at home. Safety assessments were performed during scheduled ophthalmologic follow-up visits, and prophylaxis was discontinued in the presence of clinically significant ocular toxicity or a lack of apparent therapeutic benefit.

NSAID prophylaxis was generally continued until progression to treatment-requiring ROP or 60 weeks postmenstrual age. In selected infants who had not progressed and were considered at ongoing risk of disease activity, continuation beyond 60 weeks postmenstrual age was evaluated on an individual basis according to retinal findings, safety assessments, and clinical judgment. In infants progressing to

treatment-requiring ROP managed with intravitreal anti–VEGF therapy, prophylaxis was discontinued at the time of intervention because concomitant use was not part of the routine management protocol, and evidence regarding combined administration in this setting was limited. Following laser photocoagulation, prophylaxis was continued for an additional 15 days at stage 2 dosing at the discretion of the treating specialist to address postprocedural inflammatory responses.

2.7. Variables, outcomes, and measures

The primary clinical outcomes were ROP reactivation requiring retreatment and the interval between initial intravitreal anti–VEGF administration and retreatment. Secondary clinical outcomes included the time elapsed between retreatment decision and implementation and the total number of ophthalmologic follow-up visits from initial screening through 60 weeks postmenstrual age. The economic outcomes included QALYs and total direct ROP-related healthcare costs accrued from the first ophthalmologic assessment through the end of follow-up.

Retinal regression was defined as a reduction in or resolution of plus disease, flattening of the vascular ridge, regression of extraretinal fibrovascular proliferation, and progressive retinal vascular maturation without evidence of renewed pathological angiogenic activity. Reactivation warranting retreatment was defined as recurrence or progression of plus disease, persistent or renewed neovascularization, worsening fibrovascular proliferation, extension of the avascular retina associated with active disease, or any deterioration considered to place the infant at risk of unfavorable structural progression. Retreatment decisions included retinal findings, disease zone, vascular activity, and longitudinal disease evolution during follow-up evaluations [37, 54, 55].

Baseline demographic and clinical variables collected for adjustment for potential confounding factors included sex, birth weight, gestational age, postmenstrual age at diagnosis, healthcare coverage status, oxygen therapy exposure during neonatal intensive care admission, the presence of plus disease, vitreous hemorrhage before anti-VEGF administration, NSAID prophylaxis status, prophylactic agent, and the timing of initial anti-VEGF treatment relative to diagnosis.

2.8. Cost calculation

The economic evaluation was conducted from the Colombian healthcare system perspective and included all direct medical costs associated with ROP management from the initial ophthalmologic assessment through 60 weeks postmenstrual age. Costs incurred beyond the study observation period were not included. Cost estimates were primarily derived from the national reimbursement schedule established by the Colombian Ministry of Health and Social Protection (*Decreto 2423 de 1996*) and supplemented with local pharmacy acquisition costs for medications [56]. To enhance real-world applicability, selected cost parameters were cross-validated against institutional billing records from participating centers.

Direct medical costs were estimated using observed resource utilization and included diagnostic, pharmaceutical, procedural, and hospitalization-related expenditures. Diagnostic costs included

ophthalmologic evaluations and retinal imaging. Pharmaceutical costs included those associated with prophylactic NSAIDs and intravitreal anti–VEGF therapy as well as retreatment procedures within the study time frame. Procedural costs included those for intravitreal injections, laser photocoagulation, procedure-related consumables, and institutional overhead. Hospitalization costs were incorporated when applicable.

Cost calculations distinguished between bevacizumab and ranibizumab based on their acquisition and utilization characteristics. Bevacizumab was supplied in multidose vials that permitted aseptic aliquoting for multiple intravitreal administrations, whereas ranibizumab was supplied as a single-use vial in accordance with the manufacturer's recommendations and routine clinical practice [57–60].

All monetary values were initially recorded in Colombian pesos (COP) and converted to United States dollars (USD) using the exchange rate of January 7, 2026 (1 USD = 3,727.96 COP).

2.9. QALY estimation

Health-related quality of life was quantified using QALYs calculated over a 60-week postmenstrual age horizon corresponding to the study observation period. This interval encompassed the period during which treatment-requiring ROP, disease reactivation, retreatment, and retinal stabilization were most likely to occur [28–30].

QALYs were estimated using a state-transition approach in which time spent within predefined clinical health states was multiplied by the corresponding utility value and normalized to a 365-day reference scale. Utility values ranged from 0 (death-equivalent health state) to 1 (optimal health) and were derived through the triangulation of published literature, expert clinical consensus, and cohort-specific assumptions informed by observed patterns of disease severity, treatment burden, retreatment requirements, and healthcare utilization [19, 61–64].

Because validated utility estimates for neonatal ROP remain limited, values were selected pragmatically to reflect differences in disease severity, treatment burden, retreatment requirements, and anticipated healthcare utilization. Iterative sensitivity analyses using custom-built algorithms in R for Windows version 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria) were performed to evaluate robustness across plausible utility ranges.

For early-stage ROP managed conservatively without prophylaxis, a utility value of 0.80 was assigned to reflect the generally favorable natural history of early disease while accounting for surveillance burden and prematurity-related comorbidities. Infants receiving ketorolac or nepafenac prophylaxis were assigned modestly higher utility values (0.85 and 0.90, respectively) on the basis of exploratory assumptions that reduced disease progression and lower intervention burden could translate into improved short-term health-related quality of life [41, 46–48].

Among infants who progressed to treatment-requiring advanced-stage ROP, postintervention utility values were stratified according to treatment modality and retreatment burden. Bevacizumab and

ranibizumab were assigned utility values of 0.75 and 0.70, respectively, reflecting differences in observed retreatment frequency, follow-up intensity, and healthcare utilization patterns within the study cohort [8, 11, 32, 33, 65–68].

Utility values were further adjusted downward in cases requiring retreatment to account for cumulative procedural risks, increased healthcare demands, and caregiver stress. A value of 0.50 was applied following the first retreatment, decreasing to 0.40 after a second reintervention. These decreases also reflect the expected visual and functional impact of laser ablation, including irreversible peripheral retinal damage; increased risk for high myopia, strabismus, and amblyopia; postprocedural inflammation; and prolonged recovery [13, 69, 70].

2.10. Statistical analyses

Categorical variables were summarized as frequencies and percentages, whereas continuous variables were reported as means and standard deviations. Group comparisons for categorical variables were performed using Pearson's chi-square test or Fisher's exact test when expected cell counts were fewer than five. Continuous variables were compared using independent-samples t tests or Wilcoxon rank-sum tests according to the distribution characteristics assessed through Shapiro–Wilk testing and graphical inspection.

The primary binary outcome, ROP reactivation requiring retreatment by 60 weeks postmenstrual age, was evaluated using logistic regression with a logit link. Crude relative risks and corresponding 95% confidence intervals (CIs) were calculated descriptively. Multivariable logistic regression was subsequently performed to generate adjusted odds ratios and account for potential confounding factors. The primary exposure variable was anti–VEGF treatment type (bevacizumab versus ranibizumab).

Prespecified adjustment variables selected a priori on the basis of biological plausibility and clinical relevance included NSAID prophylaxis status (none, ketorolac, or nepafenac), gestational age at birth, birth weight, postmenstrual age at diagnosis, oxygen therapy exposure during neonatal intensive care admission, presence of plus disease, vitreous hemorrhage before anti-VEGF administration, and time elapsed between diagnosis and treatment. The interaction between anti-VEGF treatment and NSAID prophylaxis was explored in prespecified analyses and retained when clinically meaningful or statistically significant.

The time to retreatment was evaluated using Kaplan–Meier survival analysis and compared between groups using the log-rank test. Cox proportional hazards regression was subsequently performed to identify predictors of retreatment timing. The results were reported as hazard ratios, 95% CIs, and two-sided p values. The proportional hazards assumption was assessed using log-log survival plots.

All the statistical analyses were performed using JMP Statistical Discovery Software version 19.0.1 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a two-sided p value < 0.05. Formal multiplicity correction was not applied because the analyses were considered exploratory and hypothesis-generating.

2.11. Probabilistic sensitivity analyses

Cost-effectiveness analyses compared bevacizumab and ranibizumab monotherapy from the Colombian healthcare system perspective. The mean total costs and QALYs together with their corresponding standard deviations, derived from the study cohort, were used as input parameters for probabilistic sensitivity analyses comprising 100,000 Monte Carlo simulations. Because the analytic horizon extended only through 60 weeks postmenstrual age, discounting of costs and QALYs was not applied [71, 72]. All the simulations were performed using R version 4.4.3.

Costs were modeled using gamma distributions to account for right-skewed nonnegative data, whereas QALYs were modeled using beta distributions bounded between 0 and 1 [71, 72]. Incremental costs (ΔCost) and incremental effectiveness (ΔEffectiveness) were calculated for each simulation as follows [73]:

$$\Delta\, Cost = Cost_{bevacizumab} - Cost_{ranibizumab}$$

$$\Delta\, Effectiveness = QALY_{bevacizumab} - QALY_{ranibizumab}$$

From each paired draw, incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB) values were derived [73]:

$$ICER = \frac{\Delta\, Cost}{\Delta\, Effectiveness}$$

$$NMB = (\text{Willingness to Pay} \times\ \Delta\, Effectiveness) - \Delta\, Cost$$

To improve the estimation stability and reduce the influence of implausible ratio inflation caused by extremely small effectiveness differences, simulations with absolute ΔEffectiveness values below 1×10^{-4} were excluded. The remaining iterations subsequently underwent winsorization at the 2.50th and 97.50th percentiles to limit the influence of extreme tail values while preserving overall variability. To further characterize residual uncertainty, 10,000 bootstrap replicates of the adjusted dataset were generated to obtain robust point estimates and percentile-based 95% confidence intervals for the ICER and NMB estimates.

Bevacizumab was considered the more cost-effective strategy when the ICER estimates remained below Colombia's willingness-to-pay threshold of USD 5,180.80 per QALY and the corresponding NMB estimates were positive [73–75]. Interpretation of simulations with negative ICER values followed standard quadrant-based cost-effectiveness decision rules, with southeast quadrant clustering indicating the dominance of bevacizumab and northwest quadrant clustering indicating the dominance of ranibizumab. The other quadrants represent trade-off scenarios for practice and policymaking [75].

The outputs were summarized using cost-effectiveness planes, cost-effectiveness acceptability curves, acceptability frontier analyses, and NMB-versus-willingness-to-pay plots to evaluate decision uncertainty

across alternative healthcare system thresholds and contexts. While point estimates and 95% CIs were derived from the filtered, winsorized, and bootstrapped iterations, graphical probabilistic outputs incorporated the complete set of nonfiltered simulations to preserve the full uncertainty distribution generated by the Monte Carlo analyses.

2.12. Subgroup analyses

Prespecified subgroup analyses were performed to evaluate whether clinical and economic outcomes associated with bevacizumab and ranibizumab varied across clinically relevant neonatal risk strata. Infants were stratified according to gestational age (< 28 weeks, 28–32 weeks, and > 32 weeks), birth weight (< 1,000 g, 1,000–1,500 g, and > 1,500 g), and NSAID prophylaxis status (none, ketorolac, or nepafenac). These categories were selected a priori on the basis of their established associations with ROP severity and progression risk [13]

Within each subgroup, retreatment rates, relative risks, mean costs, and QALYs were calculated descriptively. Subgroup-specific cost and QALY distributions were subsequently incorporated into independent Monte Carlo simulations to characterize uncertainty and evaluate potential heterogeneity in economic outcomes across neonatal risk strata.

Because subgroup analyses were exploratory and effectiveness differences were frequently negligible, NMB was prioritized over ICER for comparative interpretation across neonatal risk strata owing to its greater numerical stability and more interpretable representation of the balance between clinical benefit and healthcare-system costs. Higher NMB values were interpreted as indicating greater cost-effectiveness [73, 75, 76].

To maintain internal validity, subgroup analyses were considered descriptive and hypothesis-generating, and formal interaction testing was not incorporated into the primary multivariable models because of the modest sample size. The subgroup prevalence within the cohort was incorporated into aggregate economic projections to improve the representativeness of the observed neonatal population structure.

3. Results

3.1. Study population

A total of 131 preterm infants who received first-line intravitreal anti–VEGF monotherapy for treatment-requiring ROP were initially identified. Ten infants (7.63%) were excluded because follow-up before 60 weeks postmenstrual age was incomplete. The final analytic cohort comprised 121 infants, of whom 47 (38.84%) received bevacizumab and 74 (61.16%) received ranibizumab. The deidentified study dataset is provided in Supplementary Material 1.

3.2. Baseline characteristics

Baseline demographic and clinical characteristics are summarized in Table 1. Overall, the treatment groups were comparable with respect to sex, birth weight, gestational age, postmenstrual age at diagnosis, healthcare coverage, oxygen therapy during neonatal intensive care admission, vitreous hemorrhage before treatment, and time from diagnosis to initial intravitreal anti–VEGF therapy.

Several clinically relevant baseline imbalances were identified. Infants weighing > 1,500 g were more frequently treated with bevacizumab than with ranibizumab (51.06% vs. 32.43%; $p = 0.0412$), as were infants born at > 32 weeks of gestation (29.79% vs. 14.86%; $p = 0.0482$). Conversely, plus disease before anti-VEGF treatment was more common among infants receiving ranibizumab (27.03% vs. 10.64%; $p = 0.0300$). NSAID prophylaxis also differed between groups: nepafenac prophylaxis was more frequent among infants subsequently treated with bevacizumab (74.47% vs. 35.14%; $p < 0.0001$), whereas the absence of prophylaxis was more common among infants receiving ranibizumab (58.11% vs. 19.15%; $p < 0.0001$). These variables were included in the prespecified multivariable analyses to account for potential confounding.

3.3. Clinical outcomes

Clinical outcomes are summarized in Table 2. Overall, 39 of 121 infants (32.23%) required retreatment during follow-up. Retreatment occurred less frequently among infants treated with bevacizumab than among those treated with ranibizumab (3/47 [6.38%] vs. 36/74 [48.65%]; $p < 0.0001$), corresponding to an unadjusted relative risk of 7.62 (95% CI: 2.49–23.35) for retreatment with ranibizumab compared with bevacizumab.

Among infants requiring retreatment, the interval between the initial intravitreal anti–VEGF injection and retreatment was similar between groups (27.33 ± 14.77 days for bevacizumab vs. 22.11 ± 3.42 days for ranibizumab; $p = 0.7169$). Delays between the clinical indication for retreatment and its implementation occurred less frequently among bevacizumab-treated infants (6.38% vs. 40.54%; $p < 0.0001$). The mean number of ophthalmologic follow-up visits through 60 weeks postmenstrual age was lower in the bevacizumab group, although the difference did not reach statistical significance (5.21 ± 2.84 vs. 6.16 ± 3.16 visits; $p = 0.0566$).

The mean QALYs were similar between the treatment groups (0.39 ± 0.05 for bevacizumab vs. 0.38 ± 0.07 for ranibizumab; $p = 0.1828$). No treatment-related adverse events or deaths were documented during the study period.

3.4. Multivariate analyses

Multivariable logistic regression demonstrated that bevacizumab remained independently associated with lower odds of retreatment after adjustment for prespecified covariates (adjusted odds ratio: 0.38; 95% CI: 0.17–0.72; $p = 0.0012$). Nepafenac prophylaxis was also independently associated with lower odds of retreatment (adjusted odds ratio: 0.21; 95% CI: 0.08–0.51; $p = 0.0004$).

Cox proportional hazards regression revealed that higher gestational age at birth was independently associated with a lower hazard of retreatment (hazard ratio: 0.66 per additional week; 95% CI, 0.49–0.90; $p = 0.0081$), whereas higher postmenstrual age at diagnosis was associated with a greater hazard of retreatment (hazard ratio: 1.21 per additional week; 95% CI: 1.07–1.37; $p = 0.0028$). The proportional hazards assumption was satisfied on the basis of the log–log survival plots.

3.5. Cost-effectiveness analyses

The cost-effectiveness results are summarized in Table 3. The mean total ROP-related costs from the initial ophthalmologic assessment through 60 weeks postmenstrual age were lower among infants treated with bevacizumab than among those treated with ranibizumab (USD 1,706.10 ± 375.64 vs. USD 2,681.88 ± 750.01; $p < 0.0001$). The mean QALYs were comparable between the treatment groups (0.39 ± 0.05 vs. 0.38 ± 0.07; $p = 0.1828$).

Deterministic cost-effectiveness analysis demonstrated economic dominance of bevacizumab over ranibizumab, with an ICER of –USD 95,578.00 per QALY and an NMB of USD 1,027.59 at Colombia's willingness-to-pay threshold of USD 5,180.80 per QALY.

Probabilistic sensitivity analysis yielded a mean ICER of –USD 1,938.66 ± 307.12 per QALY (median, –USD 1,939.70; 95% CI, –USD 2,536.09 to –USD 1,341.73) and a mean NMB of USD 1,022.93 ± 3.00 (median, USD 1,022.94; 95% CI, USD 1,017.10–1,028.81). Compared with the deterministic analysis, NMB estimates demonstrated minimal variability across simulations, whereas ICER estimates exhibited substantially greater dispersion.

The probabilistic simulations revealed that 49.70% of the iterations were located in the southeast quadrant of the cost-effectiveness plane and 38.92% in the southwest quadrant (Fig. 1). Cost-effectiveness acceptability analyses estimated an 86.55% probability that bevacizumab was the more cost-effective strategy at the Colombian willingness-to-pay threshold (Fig. 2). Across the evaluated willingness-to-pay range, NMB remained positive for bevacizumab (Fig. 3). Because bevacizumab generated the greatest expected net benefit throughout the evaluated threshold range, a cost-effectiveness acceptability frontier was not constructed.

3.6. Subgroup analyses

The results of the subgroup analyses are summarized in Table 4. Across all prespecified strata for gestational age, birth weight, and NSAID prophylaxis, bevacizumab was consistently associated with lower retreatment rates, lower ROP-related costs, and comparable or higher QALYs than ranibizumab.

Among infants born before 28 weeks of gestation, no retreatment events occurred in the bevacizumab group, whereas the retreatment rate among infants treated with ranibizumab was 30.00% ($p = 0.0317$). The mean ROP-related costs were also lower for bevacizumab (USD 1,608.29 ± 60.30 vs. USD 2,654.07 ± 753.67; $p = 0.0004$). Similarly, among infants with birth weights < 1,000 g, no retreatment events occurred after bevacizumab treatment, whereas retreatment occurred in 36.36% of infants treated with

ranibizumab (p = 0.0074). The mean costs remained lower with bevacizumab (USD 1,604.39 ± 66.92 vs. USD 2,811.57 ± 776.73; p = 0.0002), and probabilistic analyses demonstrated favorable cost-effectiveness estimates.

Across the remaining gestational age and birth weight strata, bevacizumab consistently yielded lower costs and positive NMB values while maintaining comparable effectiveness. Similar findings were observed irrespective of NSAID prophylaxis status. Among infants without prophylaxis, bevacizumab was associated with lower retreatment rates (3.58% vs. 72.09%; p = 0.0047), lower mean costs (USD 1,894.37 ± 693.58 vs. USD 3,012.13 ± 699.34; p < 0.0001), and positive NMB estimates. Among infants receiving nepafenac prophylaxis, bevacizumab likewise remained associated with lower costs and favorable economic outcomes.

4. Discussion

4.1. Clinical implications of the findings

This multicenter real-world evaluation demonstrated that bevacizumab, when used as a first-line intravitreal anti–VEGF monotherapy for treatment-requiring ROP, was associated with substantially lower retreatment rates, fewer delays to retreatment, and lower direct medical costs than ranibizumab while achieving comparable short-term health-related quality of life. Collectively, these findings indicate that bevacizumab may be a high-value therapeutic option for managing advanced ROP, particularly in neonatal referral networks where continuity of follow-up and healthcare resources are limited.

The lower retreatment burden observed with bevacizumab is consistent with its greater intraocular durability and more sustained VEGF suppression reported in previous pharmacokinetic, observational, and randomized studies [8, 11, 32, 33, 65–68]. In routine clinical practice, these pharmacologic characteristics may translate into fewer reinterventions, reduced surveillance intensity, and a lower risk of delayed treatment among infants requiring prolonged ophthalmologic follow-up.

An important finding was the consistency of the treatment effect across clinically relevant neonatal risk strata. Bevacizumab was associated with lower retreatment rates and lower healthcare utilization among extremely premature infants, very low-birth-weight infants, and infants managed under various early-stage prophylactic strategies. Although these subgroup analyses should be interpreted with caution given the limited sample size within individual strata, they suggest that the observed clinical and economic advantages were not confined to a single patient subgroup.

Comparable QALYs despite substantially lower healthcare utilization provide additional insight into the clinical relevance of the findings. Similar short-term health-related quality of life was achieved with fewer retreatment procedures and lower overall resource use, suggesting that improved efficiency was not accompanied by measurable reductions in patient-centered outcomes during the study period.

These findings should be interpreted alongside the continuing uncertainty regarding the long-term systemic safety of intravitreal anti-VEGF therapy in premature infants. Although no treatment-related adverse events or deaths were documented during follow-up, the present study was not designed or powered to evaluate uncommon systemic events, neurodevelopmental outcomes, or late ocular sequelae. Consequently, treatment selection should continue to balance the demonstrated clinical and economic advantages of bevacizumab with the need for additional prospective evidence evaluating long-term safety, visual outcomes, and functional development.

4.2. Implications for healthcare resource allocation

Beyond differences in clinical effectiveness, the present findings have important implications for healthcare resource allocation. Compared with ranibizumab, bevacizumab was associated with lower retreatment rates, fewer retreatment-related delays, reduced healthcare utilization, and substantially lower direct medical costs while maintaining comparable short-term health-related quality of life. Together, these findings indicate that therapeutic selection may influence not only patient outcomes but also the efficiency with which limited healthcare resources are allocated.

Within the Colombian health system, choosing bevacizumab over ranibizumab may yield an economic advantage monetized at approximately 2.18 times the monthly national minimum salary over a 60-week postmenstrual period, underscoring the magnitude of avoidable expenditure incurred when a substantially costlier agent is selected without demonstrable clinical superiority.

The economic implications extend beyond differences in medication acquisition costs. Lower retreatment rates were accompanied by reduced demand for follow-up visits, repeat procedures, and associated healthcare services, illustrating how treatment selection can influence multiple components of neonatal care delivery. In health systems with limited specialist availability, these reductions may increase service capacity and improve timely access for additional infants requiring retinal screening, treatment, and longitudinal follow-up.

These considerations are particularly relevant in low- and middle-income countries, where shortages of trained ROP specialists, geographic barriers, fragmented referral pathways, and inconsistent adherence to follow-up frequently compromise continuity of care. Under these circumstances, therapeutic strategies that reduce the need for repeat interventions may improve the efficiency of neonatal referral networks by allowing specialized resources to be redirected toward infants with unmet clinical needs.

Economic evaluations should complement, rather than replace, individualized clinical decision-making. However, by integrating real-world clinical outcomes with healthcare utilization and direct medical costs, the present study provides decision-relevant evidence that may support health technology assessment, formulary evaluation, reimbursement discussions, and value-based resource allocation for treatment-requiring ROP.

4.3. Alignment with and contribution to existing evidence

This study is among the first real-world cost-effectiveness evaluations to directly compare bevacizumab and ranibizumab for treatment-requiring ROP. Previous pharmacoeconomic evaluations of anti–VEGF therapy have relied predominantly on evidence derived from adult retinal diseases, limiting their applicability to neonatal populations with distinct disease trajectories, follow-up requirements, and healthcare utilization patterns [16, 77–83]. By integrating real-world clinical outcomes, healthcare utilization, and direct medical costs observed during routine neonatal care, the present evaluation provides decision-relevant evidence that is specifically applicable to pediatric ophthalmology.

An additional contribution is the incorporation of ophthalmic NSAID prophylaxis into multivariable and subgroup analyses. Although topical NSAID prophylaxis remains an exploratory off-label strategy and should not be considered standard care, adjustment for this clinically relevant exposure reduced potential confounding arising from variation in early-stage disease management. It enabled evaluation of anti-VEGF effectiveness within a real-world treatment environment. Future prospective studies should further investigate the interaction between early-stage prophylactic strategies and outcomes following treatment-requiring ROP.

4.4. Methodological considerations for economic evaluation

The probabilistic analyses highlighted the importance of appropriately characterizing decision uncertainty when evaluating interventions with relatively small differences in health outcomes. Although deterministic and probabilistic analyses consistently demonstrated the economic advantage of bevacizumab, compared with NMB, ICER estimates exhibited substantially greater variability despite nearly identical underlying clinical conclusions.

This observation reflects a recognized methodological characteristic of ICERs. When health gains are discrete or negligible, minor variations in QALY estimates may produce disproportionately large changes in ICER values despite minimal differences in overall decision uncertainty. In contrast, NMB integrates costs and health outcomes within a willingness-to-pay framework, producing estimates that are generally more numerically stable and readily interpretable for healthcare decision makers [73, 76, 84].

These considerations may be particularly relevant in neonatal medicine, where short analytic horizons, relatively small sample sizes, and favorable overall outcomes frequently result in modest incremental QALY differences between competing interventions. Under these circumstances, complementary reporting of both ICER and NMB may provide a more comprehensive assessment of value than either metric alone by simultaneously preserving international reporting standards and facilitating interpretation for reimbursement and resource-allocation decisions.

Rather than replacing conventional ICER-based analyses, the present findings support the complementary use of NMB to strengthen the interpretation of economic evaluations in areas such as neonatal care, where an intervention may yield a significant impact on health-related quality of life and disability prevention, yet it is only slightly superior to other available strategies when quantified.

Additional methodological research across larger multicenter datasets and other pediatric conditions would help determine the generalizability of these observations.

4.5. Strengths, limitations, and future research

This study has several important strengths. By integrating clinical effectiveness, healthcare utilization, direct medical costs, QALYs, probabilistic sensitivity analyses, and prespecified subgroup analyses, the evaluation provides a comprehensive assessment of value that is directly relevant to healthcare resource allocation and decision-making.

Several limitations should also be considered. First, the retrospective observational design limits causal inference and remains susceptible to residual confounding despite standardized clinical management, prespecified multivariable adjustment, and extensive sensitivity analyses. Second, all the participating infants were managed by a single retina specialist, reducing interobserver variability while potentially limiting generalizability to healthcare settings with different clinical practices or referral pathways. Third, QALY estimation incorporated utility values derived from published evidence, expert consensus, and model assumptions because validated preference-based utility estimates for neonatal ROP remain limited. Fourth, the analytic horizon was restricted to 60 weeks postmenstrual age and therefore did not capture long-term visual function, neurodevelopment, refractive outcomes, or lifetime healthcare costs. Finally, the evaluation adopted a healthcare-system perspective and did not incorporate indirect costs borne by families or society.

Future research should prioritize prospective multicenter studies with longer follow-up periods that integrate clinical, economic, neurodevelopmental, and functional visual outcomes. Additional evaluations incorporating societal costs and formal budget impact analyses would complement the present findings by supporting reimbursement decisions and implementation planning across diverse healthcare systems. An investigation of emerging therapeutic strategies, including biosimilar anti-VEGF agents and optimized treatment protocols, may further refine the value-based management of treatment-requiring ROP.

5. Conclusions

In this multicenter real-world evaluation of treatment-requiring ROP, bevacizumab demonstrated greater economic value than ranibizumab did over a 60-week postmenstrual age horizon. Compared with ranibizumab, bevacizumab was associated with lower retreatment rates, fewer delays in retreatment, lower direct medical costs, and comparable short-term health-related quality of life. These findings remained consistent across clinically relevant neonatal risk strata and were supported by deterministic and probabilistic economic analyses.

These findings suggest that bevacizumab may represent a high-value therapeutic option for the management of treatment-requiring ROP, particularly in healthcare systems with limited resources and limited specialist capacity, despite lacking of regulatory approval globally as with ranibizumab.

Prospective multicenter studies with longer follow-up periods are warranted to evaluate long-term visual, neurodevelopmental, safety, and economic outcomes and to further inform health technology assessment and resource-allocation decisions.

Abbreviations

anti-VEGF, anti-vascular endothelial growth factor; CI, confidence interval; COP, Colombian peso; ICD-10, International Classification of Diseases, Tenth Revision; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; NSAID, nonsteroidal anti-inflammatory drug; QALY, quality-adjusted life-year; ROP, retinopathy of prematurity; USD, United States dollar; VEGF, vascular endothelial growth factor.

Declarations

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Conflicts of Interest: The authors declare no financial, personal, or professional conflicts of interest that could have influenced the study design, analysis, or presentation of the results.

Ethical Approval: This study was conducted by microscopIA, a scientific research and innovative institution recognized by the Colombian Ministry of Science, Technology, and Innovation (Call 984, 2021). Ethics approval was obtained from the microscopIA Institutional Review Board (Approval OPH-001). Written informed consent for all clinical procedures was obtained from parents or legal guardians in accordance with the Declaration of Helsinki and institutional protocols.

Consent to Participate: Not applicable.

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Availability of Data, Materials, and Code: The dataset used in the analyses was submitted with this manuscript as supplementary material. Any other resources are available from the corresponding author upon reasonable request.

Author Contributions: Marudys Stella Mestra Burgos oversaw patient care and contributed to clinical data collection and securing permissions from the facilities for data collection. Jorge Racedo conceptualized the study, supervised all the methodological phases, oversaw the analytical design, served as the study guarantor, led the clinical and health-economic analyses, contributed to quality control, secured resources, managed administrative decisions, and drafted the manuscript. All remaining authors contributed to data collection, curation, quality control, and/or interpretation of the results. All the authors reviewed and approved the final version for submission.

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Tables

Tables are available in the Supplementary Files section.

Figures

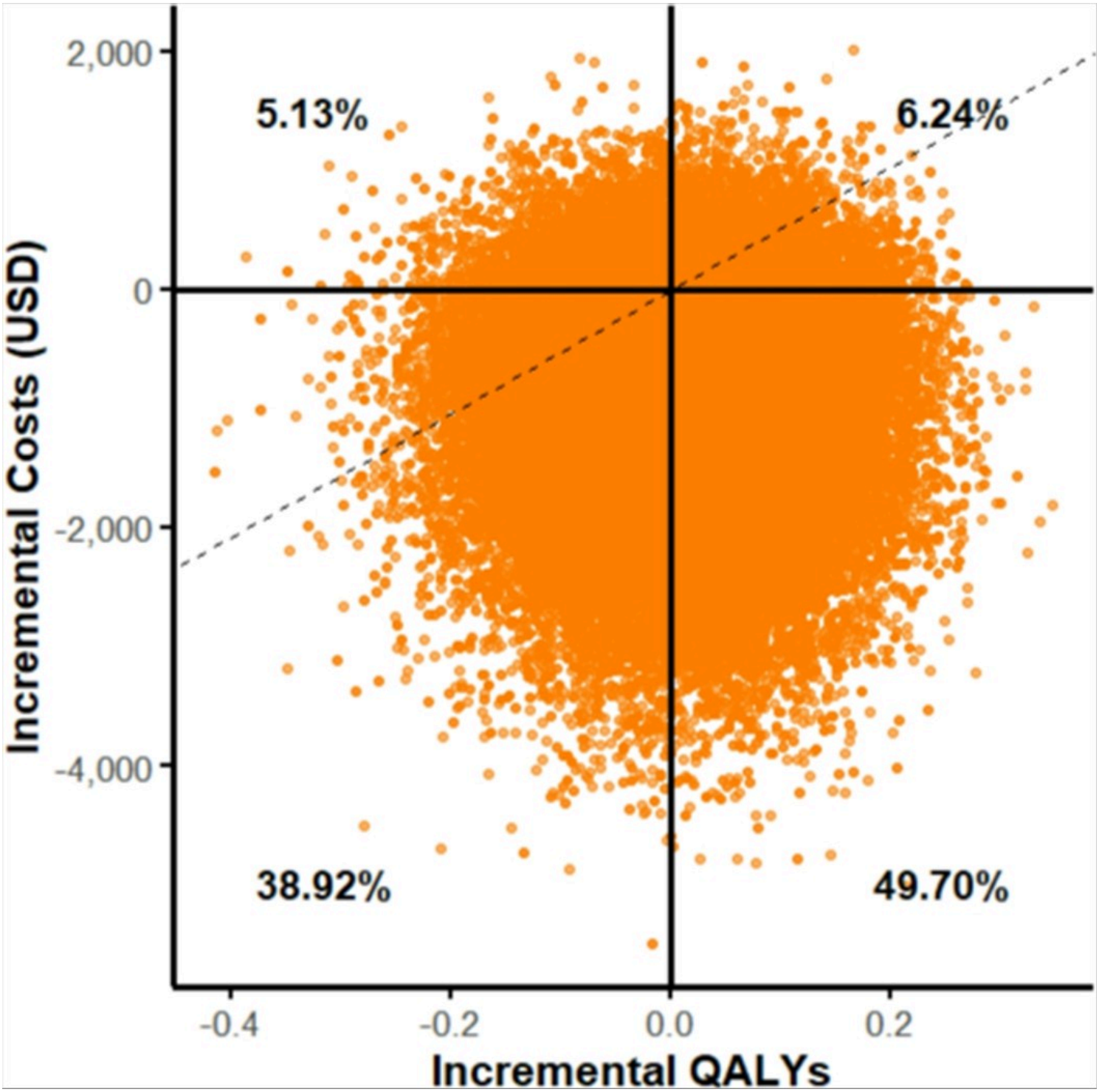


Figure 1

Cost-effectiveness plane. Scatterplot of 100,000 Monte Carlo simulations depicting incremental costs (USD) versus incremental effectiveness (QALYs) for bevacizumab compared with ranibizumab. The majority of simulations (49.70%) fall in the southeast quadrant, indicating dominance (greater effectiveness and lower cost). The percentages in each quadrant represent the proportion of iterations. The dashed line represents Colombia's willingness-to-paythreshold.

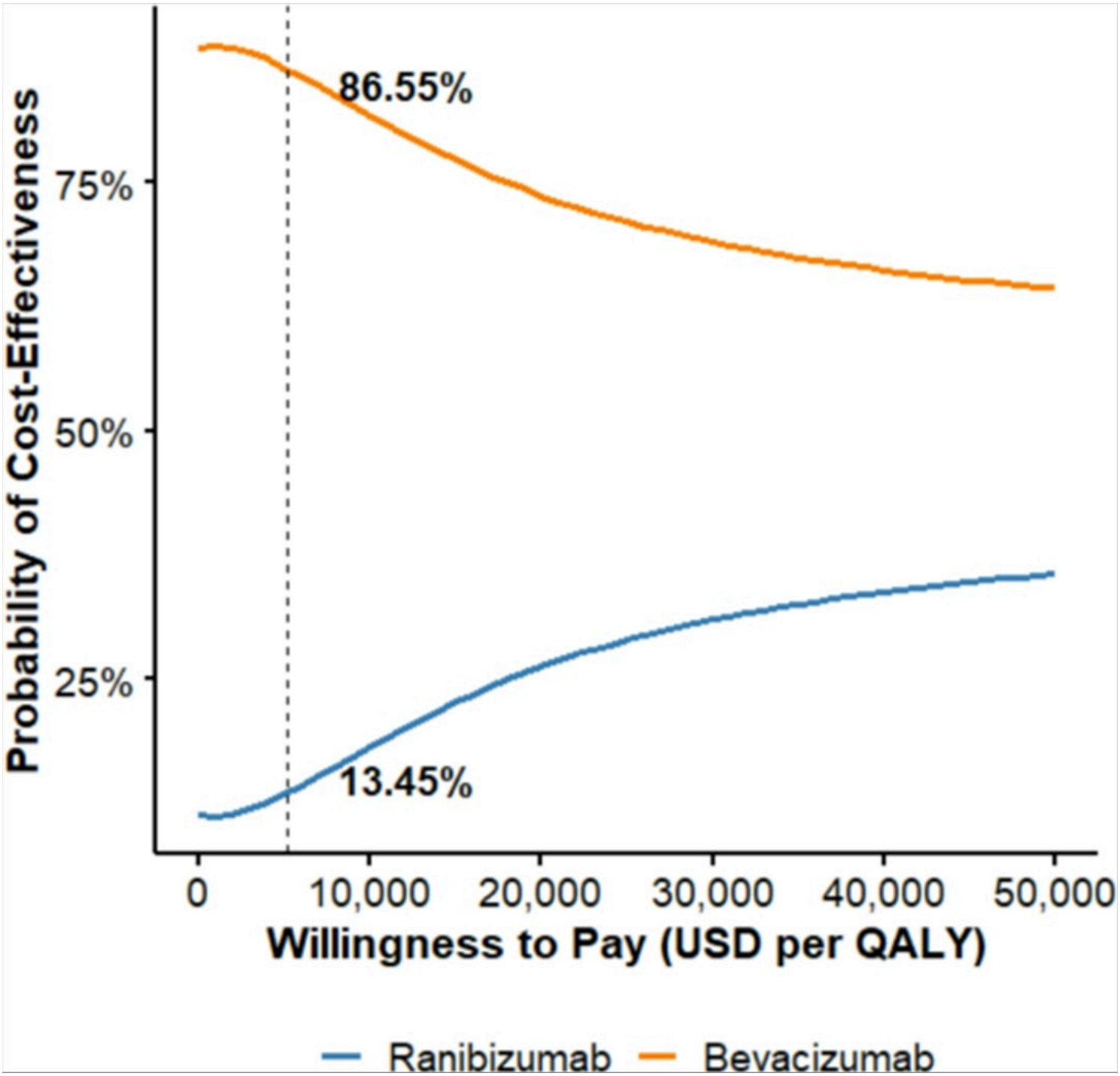


Figure 2

Cost-effectiveness acceptability curves. Probability that bevacizumab (orange) or ranibizumab (blue) is the most cost-effective strategy across a range of willingness-to-paythresholds. At Colombia's threshold, bevacizumab had an 86.55% probability of being the most cost-effective anti-VEGF agent, reflecting robust economic dominance.

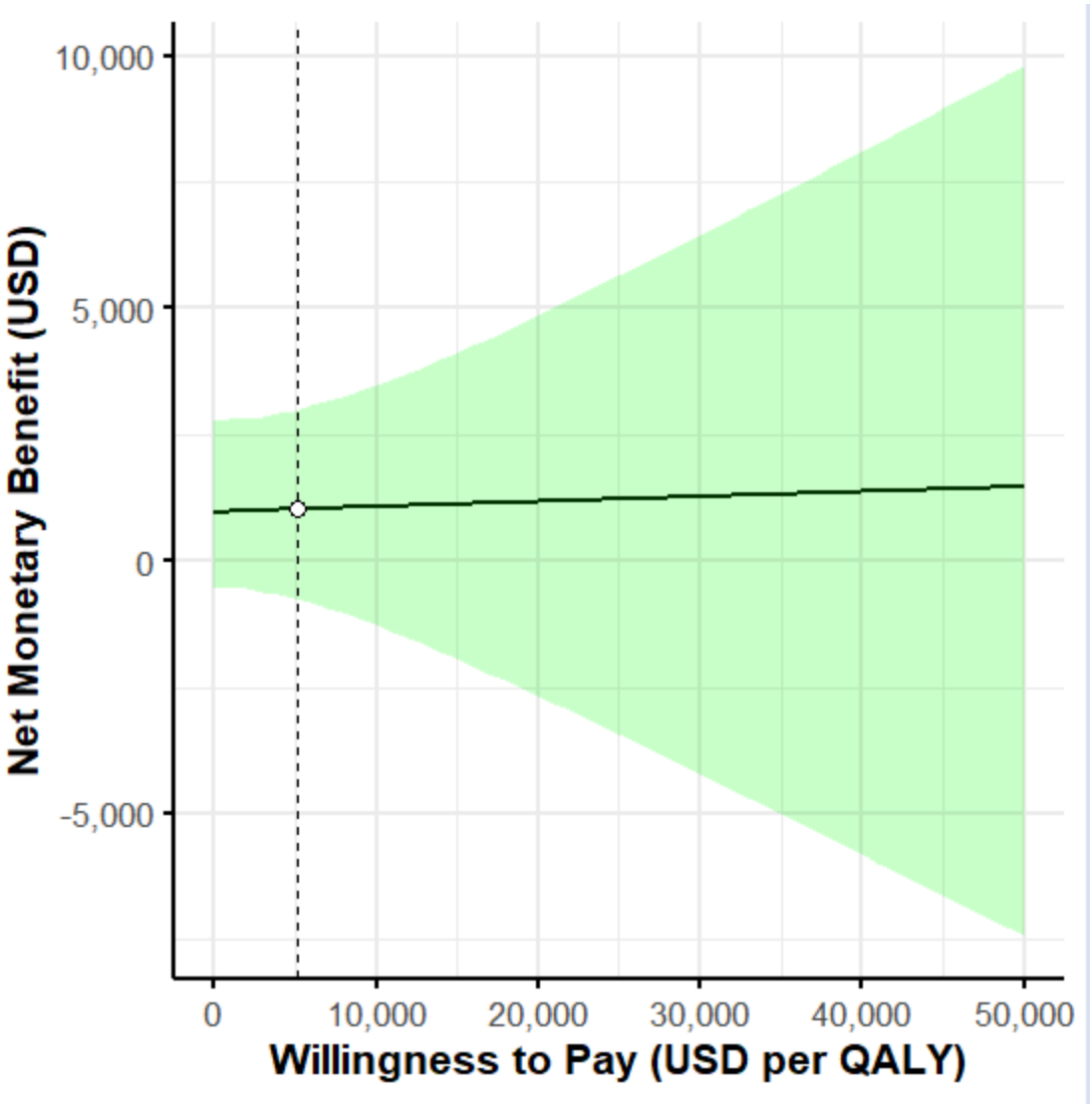


Figure 3

NMB vs. willingness-to-pay thresholds Mean NMB plotted against willingness-to-pay thresholds, with 95% CIs shaded in green (after denominator filtering, winsorization, and bootstrapping). Bevacizumab consistently increased NMB with increasing willingness to pay, indicating superior robustness in terms of cost-effectiveness.

Supplementary Files

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- SupplementaryMaterial1.xlsx
- Tables.docx