Clinical & Experimental Ophthalmology

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Clinical & Experimental Ophthalmology

ORIGINAL ARTICLE-CLINICAL SCIENCE OPEN ACCESS

Impact of Race on the Outcomes of Retinoblastoma Treated With Primary Enucleation: A Global Study of 1426 Patients

Swathi Kaliki[1] | Vijitha S. Vempuluru[1] | Alia Ahmad[2] | Jesse L. Berry[3,4] | Rosdali Diaz-Coronado[5,6] | Maya Eiger-Moscovich[7] | Ido Didi Fabian[8] | Hans Grossniklaus[9] | G. Baker Hubbard III[9] | Mona Mohammad[10] | Jacob Pe'er[7] | M. Ashwin Reddy[11] | Mandeep S. Sagoo[11,12] | Carol L. Shields[13] | Sandra E. Staffieri[14,15,16,17] | Mika Tanabe[18] | Tatiana Ushakova[19,20] | Yacoub A. Yousef[10] | High-Risk Retinoblastoma Collaborative Study Group

[1]The Operation Eyesight Universal Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India | [2]University of Child Health Sciences, Children's Hospital, Lahore, Pakistan | [3]Children's Hospital Los Angeles & USC Roski Eye Institute, Los Angeles, California, USA | [4]Keck School of Medicine, Los Angeles, California, USA | [5]Pediatric Oncology Department, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru | [6]Universidad Peruana Cayetano Heredia, Lima, Peru | [7]Hadassah Medical Center, Jerusalem, Israel | [8]Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel | [9]Emory University School of Medicine, Atlanta, Georgia, USA | [10]King Hussein Cancer Center, Amman, Jordan | [11]Royal London Hospital, Barts Health NHS Trust, London, UK | [12]Moorfields Eye Hospital NHS Foundation Trust, London, UK | [13]Ocular Oncology Service, Wills Eye Hospital, Philadelphia, Pennsylvania, USA | [14]Department of Ophthalmology, Royal Children's Hospital, Victoria, Australia | [15]Murdoch Children's Research Institute, Melbourne, Australia | [16]Centre for Eye Research Australia, Royal Victorian eye and Ear Hospital, Melbourne, Australia | [17]University of Melbourne, Melbourne, Australia | [18]Kyushu University, Fukuoka, Japan | [19]Department of Surgical Methods of Treatment With Chemotherapy No. 1 (Head and Neck Tumors), N. N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation | [20]L.A. Durnov Department of Pediatric Oncology of the Russian Medical Academy of Continuing Professional Education, Moscow, Russian Federation

Correspondence: Swathi Kaliki (kalikiswathi@yahoo.com)

Received: 23 August 2024 | **Revised:** 28 November 2024 | **Accepted:** 7 December 2024

Funding: This study was Supported by The Operation Eyesight Universal Institute for Eye Cancer (SK), Hyderabad Eye Research Foundation (SK), Hyderabad, India; and Prateek Menezes Memorial Foundation, Goa, India. The funders had no role in preparing, reviewing, or approving the manuscript.

Keywords: global study | high-risk features | histopathological features | race | retinoblastoma

ABSTRACT

Background: To evaluate the clinical presentation, pathological features and outcomes of retinoblastoma based on the race of origin in a global cohort of patients.

Methods: Retrospective collaborative study of 1426 patients who underwent primary enucleation for retinoblastoma.

Results: Patients were grouped into Caucasians ($n = 231$, 16%), Asians ($n = 841$, 59%), Hispanics ($n = 226$, 16%), Arabs ($n = 96$, 7%) and Others (Africans, African Americans, Indigenous Australians; $n = 32$, 2%) cohorts. On histopathology, massive choroidal invasion was higher in Asians (30%) and Hispanics (26%) than Caucasians (15%, $p < 0.001$). Post-laminar optic nerve invasion was higher in Asians (28%), Hispanics (20%) and Others (9%) than Caucasians (11%, $p < 0.001$). At a mean follow-up of 41 months (median, 35 months; range, < 1–149 months), tumour recurrence and metastasis-related death was higher in Hispanics (9% and 12%, respectively), Asians (4% and 13%, respectively) and Others (6% and 6%, respectively). Multivariate Cox proportional hazards analysis of outcomes based on race with 8th edition AJCC pT stage and adjuvant therapy as covariates revealed 6.8 times greater risk for orbital tumour recurrence in Hispanics compared to Caucasians ($p = 0.010$) and 3.2 times risk hazards for metastasis-related death in Hispanics and Asians compared to Caucasians ($p = 0.028$ and $p = 0.038$, respectively).

Conclusion: The histopathological features in primarily enucleated eyes with retinoblastoma vary with race. Despite adjusting for tumour staging and adjuvant treatment, race remains an independent predictor of outcomes, including orbital tumour recurrence and metastasis-related death. A stringent follow-up and a more aggressive treatment approach is recommended in Asians and Hispanics who manifest high-risk histopathological features.

1 | Introduction

The disparity in cancer survival from retinoblastoma may be influenced by various factors such as socioeconomic factors, including income, insurance coverage, health literacy, cultural factors, healthcare access and quality of care, age at diagnosis and tumour staging at presentation [1–5]. In a prospective analysis of 4064 retinoblastoma patients from 149 countries, death was 17 times higher in children from low-income countries compared to high-income countries [1]. In this cohort, children from low-income countries were predominantly from pigmented races, while children from high-income countries were mainly from non-pigmented races. However, the influence of race as an independent factor was not studied directly; thus, preventing any definitive conclusions about the impact of race on survival outcomes.

Various reports have shown racial/ethnic disparity in cancer survival [6–11]. The racial disparity in cancer outcomes may not only be influenced by modifiable socioeconomic/socioenvironmental/lifestyle factors and healthcare access but also by certain non-modifiable factors such as tumour biology and genetic ancestry. The impact of race on the outcomes of retinoblastoma is not known. Herein, we investigate the influence of race on outcomes in patients who underwent primary enucleation for retinoblastoma, focusing on understanding the tumour's biological behaviour through histopathological analysis.

2 | Methods

This is a retrospective intercontinental collaborative study from the High-risk Retinoblastoma Collaborative Study Group. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [12]. Institutional review board and ethics committee approval was obtained from the participating centres. The de-identified patient data was shared with the principal investigator, SK, who collated and validated the data. The study adhered to the tenets of the Declaration of Helsinki.

All retinoblastoma patients who underwent primary enucleation from 2011 to 2020 at the participating centres were included in this study. Those patients who underwent globe-salvage therapies or secondary enucleation or those with inadequate histopathology data post-primary enucleation were excluded from the study.

Demographic data, including age at presentation, sex, gender and race; clinical details, including heredity pattern, tumour laterality, presenting complaints and tumour details, were noted. The tumours were classified based on the International Classification of Retinoblastoma (ICRB) [13], International Intraocular Retinoblastoma Classification (IIRC) [14] and 8th edition of the American Joint Committee on Cancer (AJCC) [15]. Date of primary enucleation and the interval between presentation and primary enucleation were noted. Histopathology data, including tumour growth pattern, tumour differentiation and tumour invasion into the ocular structures, was noted. Based on the histopathology data, the tumours were classified according to pTNM stage [15]. Adjuvant treatment details, including intravenous chemotherapy, radiotherapy or palliative care, were noted. The outcomes, including orbital tumour recurrence and metastasis-related death, were noted.

The study cohort was divided into four groups (Caucasians, Asians, Hispanics, Arabs or Others) based on the parent-reported race. White Americans, White Europeans, Israeli Jews and White Australians were classified as "Caucasians," and the category of "Others" included African Americans, Africans and Indigenous Australians.

2.1 | Statistical Analysis

Data was entered and compiled using Microsoft Excel. The statistical analysis was performed using IBM SPSS Statistics, version 29.0.2.0 (20). Demographics, presenting features, clinical tumour staging, individual histopathological features, pathological staging, treatment and outcomes were compared based on race. Continuous data was expressed as mean, median and range. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to check the normality of the distribution of continuous data, based on which continuous variables with normal distribution were analysed using the ANOVA (parametric) test and continuous variables with non-normal distribution were analysed using the Kruskal–Wallis (non-parametric) test. Categorical data was expressed as proportions and analysed using the Chi-square test. Pathological features were compared within the subgroups of 8th edition AJCC cT stages based on race. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify predictors (race, pT stage, adjuvant therapy) of orbital tumour recurrence and metastasis-related death. Kaplan–Meier analysis was performed to estimate the recurrence-free survival and overall survival based on race. A p-value of < 0.05 was considered statistically significant and adjusted by applying the Bonferroni correction for multiple comparisons. Post hoc analysis was performed to assess the difference between cohorts by pair-wise comparisons.

3 | Results

A total of 1426 patients from 16 participating centres from 10 countries (Australia, Bangladesh, India, Israel, Japan, Jordan, Pakistan, Peru, Russia, United Kingdom and United States of America) of five continents (Asia, Australia, Europe, North

TABLE 1 | Analysis of 1426 patients with retinoblastoma treated with primary enucleation based on race: demographics and clinical features.

Feature	Caucasians $n=231$, n (%)	Asians $n=841$, n (%)	Hispanics $n=226$, n (%)	Arabs $n=96$, n (%)	Others $n=32$, n (%)	p
Age at presentation (months)						
Mean (median, range)	29 (25, 1–127)	30 (25, 11–120)	29 (27, 1–117)	28 (24, <1–103)	28 (24, <1–143)	0.744[r]
Gender						
Male	115 (50)	469 (56)	115 (51)	47 (49)	11 (34)	
Female	116 (50)	372 (44)	111 (49)	49 (21)	21 (66)	0.060
Hereditary pattern						
Sporadic	216 (94)	812 (97)	218 (96)	73 (76)	27 (84)	
Familial	15 (6)	27 (3)	8 (4)	24 (24)	5 (16)	<0.001[a]
Tumour laterality						
Unilateral	215 (93)	685 (81)	208 (92)	70 (73)	26 (81)	
Bilateral	16 (7)	156 (19)	18 (8)	26 (27)	6 (19)	<0.001[b]
Presenting complaint						
Leukocoria	152 (66)	577 (69)	168 (74)	67 (70)	29 (91)	0.026[c]
Strabismus	43 (19)	74 (9)	32 (14)	42 (44)	2 (6)	<0.001[d]
Others	58 (25)	224 (27)	51 (23)	16 (17)	1 (3)	0.009[e]
Duration of symptoms (months)						
Mean (median, range)	3 (1, <1–25)	4 (2, <1–51)	4 (2, <1–36)	5 (4, 0–9)	4 (3, <1–36)	<0.001[s,f]
Intraocular pressure (mm Hg)						
Mean (median, range)	20 (15, 4–55)	18 (12, 0–56)	28 (25, 6–62)	34 (19, 18–65)	26 (25, 5–51)	<0.001[s,g]
Clinical features						
Megalocornea	5 (2)	72 (9)	2 (1)	0 (0)	6 (5)	0.007[h]
Secondary glaucoma	65 (28)	245 (29)	17 (8)	1 (1)	15 (12)	<0.001[i]
Aqueous seeds	17 (7)	97 (12)	11 (5)	11 (11)	2 (6)	0.020[j]
Iris neovascularisation	98 (42)	221 (26)	14 (6)	9 (9)	11 (34)	<0.001[k]
Hyphema	4 (2)	49 (6)	11 (5)	5 (5)	0 (0)	0.082
Ectropion uveae	15 (6)	131 (16)	4 (2)	5 (5)	5 (16)	<0.001[l]
Cataract	5 (2)	56 (7)	3 (1)	5 (5)	1 (3)	0.003[m]
Orbital pseudocellulitis	6 (3)	39 (5)	0 (0)	6 (0)	0 (0)	0.005[n]
Tumour classification						
ICRB (Philadelphia version)						
Group A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Group B	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Group C	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	
Group D	26 (12)	72 (9)	80 (36)	30 (31)	1 (3)	
Group E	191 (87)	765 (91)	142 (64)	66 (69)	30 (97)	<0.001[o]

(Continues)

TABLE 1 | (Continued)

Feature	Caucasians $n=231$, n (%)	Asians $n=841$, n (%)	Hispanics $n=226$, n (%)	Arabs $n=96$, n (%)	Others $n=32$, n (%)	p
IIRC (CHLA version)						
Group A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Group B	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Group C	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	
Group D	47 (20)	97 (12)	85 (64)	32 (42)	3 (10)	
Group E	182 (79)	744 (88)	48 (36)	44 (58)	28 (90)	<0.001[p]
8th edition AJCC classification						
cT2	120 (52)	239 (31)	175 (77)	19 (79)	19 (59)	
cT3	104 (45)	488 (63)	51 (23)	5 (21)	13 (41)	
cT4b	7 (3)	51 (7)	0 (0)	(0)	0 (0)	<0.001[q]

Abbreviations: AJCC = American Joint Committee on Cancer; CHLA = Children's Hospital of Los Angeles; ICRB = International Classification of Retinoblastoma; IIRC = International Intraocular Retinoblastoma Classification.
[a]Post hoc analysis showed that Arabs were significantly different from Caucasians, Asians and Hispanics; Others were significantly different from Asians and Hispanics.
[b]Post hoc analysis showed that Caucasians were significantly different from Asians and Arabs.
[c]Post hoc analysis showed that Caucasians were significantly different from Others.
[d]Post hoc analysis showed that Caucasians were significantly different from Asians and Arabs; Arabs were significantly different from Asians, Hispanics, and Others.
[e]Post hoc analysis showed that Asians were significantly different from Others.
[f]Post hoc analysis showed that Caucasians were significantly different from Hispanics, Arabs and Others; Asians were significantly different from Hispanics and Arabs; Hispanics were different from Arabs.
[g]Post hoc analysis showed that Caucasians were significantly different from Asians, Hispanics, Arabs and Others; Asians were significantly different from Arabs; Arabs were significantly different from Hispanics and Others.
[h]Post hoc analysis showed that Caucasians were significantly different from Asians.
[i]Post hoc analysis showed that Asians were significantly different from Hispanics.
[j]Post hoc analysis showed that Asians were significantly different from Hispanics.
[k]Post hoc analysis showed that Caucasians were significantly different from Asians, Hispanics and Arabs; Asians were different from Hispanics and Arabs; Hispanics were different from Others.
[l]Post hoc analysis showed that Caucasians were significantly different from Asians; Asians were different from Hispanics; Hispanics were different from Others.
[m]Post hoc analysis showed that Asians were significantly different from Hispanics; Hispanics were significantly different from Arabs.
[n]Post hoc analysis showed that Asians were significantly different from Hispanics; Hispanics were significantly different from Arabs.
[o]Post hoc analysis showed within Group D and E, Caucasians were significantly different from Hispanics and Arabs; Others were significantly different from Hispanics and Arabs.
[p]Post hoc analysis showed within Group D and E, Caucasians were significantly different from Asian, Hispanics and Arabs; Asians were significantly different from Hispanics and Arabs; Hispanics were significantly different from Arabs and Others; Arabs were significantly different from Others.
[q]Post hoc analysis showed within Stages cT2 and cT3, Caucasians were significantly different from Asians and Hispanics; Asians were significantly different from Hispanics, Arabs and Others. Within Stage cT4, Asians were significantly different from Hispanics.
[r]ANOVA.
[s]Kruskal Wallis test.

America and South America) were included in this study. Based on the parent-reported race, the patients were grouped as Caucasians ($n=231$, 16%), Asians ($n=841$, 59%), Hispanics ($n=226$, 16%), Arabs ($n=96$, 7%), African Americans ($n=29$, 2%), Africans (n = 2, <1%) and Indigenous Australian ($n=1$, <1%) races. Based on the distribution frequency, the latter three races were included into the 'Others' cohort, comprising 32 (2%) patients. Asian cohort included 556 patients from India, 62 from Bangladesh, 181 from Pakistan and 15 from Japan.

The demographics and clinical details are listed in Table 1. Bilaterality was the highest in Arabs (27%), significantly different from Caucasians (7%, $p<0.001$). Group E tumours were highest in Asians compared to the rest of the races based on ICRB and IIRC classifications. Based on the 8th edition of AJCC, T2b was the most common tumour stage in all races. Histopathology details are listed in Table 2. Endophytic tumour pattern was common in Caucasians (39%), Asians (50%) and Hispanics (58%), while the mixed endophytic-exophytic tumours were more common in the Arabs (38%) and "Others" cohorts (40%; $p<0.001$). Moderately differentiated tumours were common in Caucasians (32%), Asians (39%) and Hispanics (45%), while well-differentiated tumours were more common in Arabs (59%) and poorly differentiated tumours were more common in the "Others" cohort (72%; $p<0.001$). Massive choroidal infiltration was more common in Asians (30%) and Hispanics (26%) than Caucasians (15%, $p<0.001$). Post-laminar optic nerve infiltration was more common in Asians (28%), Hispanics (20%) and Others (34%) when compared to Caucasians (11%, $p<0.001$). Isolated prelaminar invasion was more common in Caucasians (38%) than in Asians (18%) and Arabs (28%, $p<0.001$). Combined pre-laminar/laminar optic nerve infiltration and minor choroidal invasion were more common in Caucasians (36%) compared to Asians (20%, $p<0.001$).

The comparison of histopathological features between races within each 8th edition AJCC clinical stage also revealed significant differences (Table 3). Tumour growth patterns varied within cT2 ($p<0.001$), cT3 ($p=0.008$) and cT4 ($p=0.034$) stages, and

TABLE 2 | Analysis of 1426 patients with retinoblastoma treated with primary enucleation based on race: histopathology features.

Feature	Caucasians $n=231$, n (%)	Asians $n=841$, n (%)	Hispanics $n=226$, n (%)	Arabs $n=96$, n (%)	Others $n=32$, n (%)	p
Tumour growth pattern						
Endophytic	83 (39)	405 (50)	118 (58)	32 (35)	4 (13)	
Exophytic	51 (24)	167 (21)	37 (18)	19 (21)	13 (42)	
Mixed endophytic-exophytic	69 (33)	205 (26)	47 (23)	35 (38)	14 (45)	
Diffuse infiltrating	8 (4)	20 (2)	3 (1)	6 (7)	0 (0)	<0.001[a]
Tumour differentiation						
Well-differentiated	30 (14)	150 (18)	14 (7)	54 (59)	2 (6)	
Moderately differentiated	68 (32)	319 (39)	94 (45)	11 (12)	6 (18)	
Poorly differentiated	58 (27)	279 (34)	89 (43)	22 (24	23 (72)	
Undifferentiated	56 (26)	54 (7)	12 (6)	5 (5)	1 (3)	<0.001[b]
Tumour infiltration						
Aqueous seeds	23 (10)	108 (13)	39 (17)	12 (12)	2 (6)	0.3477
Iris	12 (5)	84 (10)	9 (4)	8 (8)	1 (3)	0.011[c]
Trabecular meshwork	11 (5)	45 (5)	6 (3)	6 (6)	1 (3)	0.487
Schlemm's canal	5 (2)	34 (4)	2 (1)	6 (6)	0 (0)	0.037[d]
Ciliary body	12 (5)	62 (7)	17 (8)	7 (7)	3 (9)	0.793
Choroid	113 (49)	370 (44)	126 (56)	46 (48)	15 (47)	0.035[e]
Minor	79 (34)	114 (14)	67 (30)	20 (21)	7 (22)	<0.001[f]
Massive	34 (15)	256 (30)	59 (26)	26 (27)	8 (25)	<0.001[g]
Optic nerve	156 (68)	568 (68)	161 (71)	49 (51)	25 (78)	0.005[h]
Prelaminar	87 (38)	149 (18)	54 (24)	18 (28)	11 (61)	<0.001[i]
Laminar	35 (15)	127 (15)	40 (18)	15 (19)	1 (5)	0.136
Post-laminar	26 (11)	238 (28)	45 (20)	16 (17)	10 (34)	<0.001[j]
Optic nerve transection	8 (3)	54 (6)	22 (10)	0 (0)	3 (9)	0.005[k]
Combined prelaminar/laminar optic nerve and minor choroid	83 (36)	166 (20)	68 (30)	21 (22)	10 (31)	<0.001[l]
Sclera	6 (3)	46 (5)	14 (6)	3 (3)	1 (3)	
Partial thickness	6 (3)	36 (4)	14 (6)	3 (3)	1 (3)	
Full thickness	0 (0)	10 (1)	0 (0)	0 (0)	0 (0)	0.174
Extrascleral tissue	3 (1)	35 (4)	8 (4)	1 (1)	0 (0)	0.110
8th edition AJCC staging						
pT1	118 (51)	371 (44)	102 (45)	52 (54)	12 (37)	
pT2	55 (24)	65 (8)	30 (13)	11 (12)	4 (13)	

(Continues)

TABLE 2 | (Continued)

Feature	Caucasians $n=231$, n (%)	Asians $n=841$, n (%)	Hispanics $n=226$, n (%)	Arabs $n=96$, n (%)	Others $n=32$, n (%)	p
pT3	49 (21)	332 (40)	70 (31)	32 (33)	13 (41)	
pT4	9 (4)	73 (9)	24 (11)	1 (1)	3 (9)	<0.001[m]

Abbreviation: AJCC = American Joint Committee on Cancer.
[a]Post hoc analysis showed that the prevalence of endophytic tumours was significantly different between Caucasians vs. Asians, Hispanics and Others; and between Asians vs. Arabs and Others. The prevalence of exophytic tumours was significantly different between Hispanics vs. Others. The prevalence of mixed endophytic-exophytic tumours and diffuse infiltrating tumours was not significantly different between the groups.
[b]Post hoc analysis showed that the prevalence of well-differentiated tumours was significantly different between Caucasians vs. Arabs; Asians vs. Hispanics and Arabs; Arabs vs. Others. The prevalence of moderately differentiated tumours was significantly different between Caucasians vs. Arabs. The prevalence of poorly differentiated tumours was significantly different between Caucasians vs. Hispanics and Others; between Asians vs. Others; between Hispanics vs. Arabs and Others; between Arabs vs. Others.
[c]Post hoc analysis showed that Asians were significantly different from Hispanics.
[d]Post hoc analysis showed that Hispanics were significantly different from Arabs.
[e]Post hoc analysis showed that Asians were significantly different from Hispanics.
[f]Post hoc analysis showed that Asians were significantly different from Caucasians and Hispanics.
[g]Post hoc analysis showed that Caucasians were significantly different from Asians and Hispanics.
[h]Post hoc analysis showed that Arabs were significantly different from Caucasians, Asians and Hispanics.
[i]Post hoc analysis showed that Caucasians were significantly different from Asians and Arabs.
[j]Post hoc analysis showed that Caucasians were significantly different from Asians, Hispanics, and Others.
[k]Post hoc analysis showed that Arabs were significantly different from Hispanics and Others.
[l]Post hoc analysis showed that Caucasians were significantly different from Asians.
[m]Post hoc analysis showed that the prevalence of pT1 tumours was no different between the races; the prevalence of pT2 tumours was significantly different between Caucasians vs. Asians and Hispanics; the prevalence of pT3 tumours was significantly different between Caucasians vs. Asians; the prevalence of pT4 tumours was significantly different between the Hispanics and Arabs.

Aqueous seeds were more common in Hispanics in both AJCC cT2 and cT3 stages ($p<0.001$). Tumour differentiation also varied between the races within the cT2 and cT3 stages. Massive choroidal invasion was less common in Caucasians (14%) compared to Asians (31%), Hispanics (35%) and Others (44%) ($p=0.002$) in the AJCC cT3 stage. Post-laminar optic nerve infiltration was less common in Caucasians compared to Asians, Hispanics and Others in the AJCC cT2 ($p<0.001$) and cT3 ($p<0.001$) stages. Combined pre-laminar/laminar optic nerve infiltration and minor choroidal invasion were more common in Caucasians (47%) compared to Asians (22%) and Hispanics (33%, $p<0.001$) in the AJCC cT3 stage. There were limited patients in Arabs ($n=5$) and Others ($n=12$) cohorts in the cT3 stage category.

At a mean follow-up of 41 months (median, 35 months; range, <1–149 months), 2 (1%) Caucasians, 36 (4%) Asians, 20 (9%) Hispanics, no Arabs and 2 (2%) of the Others cohort had orbital tumour recurrence and 5 (2%) Caucasians, 110 (13%) Asians, 28 (12%) Hispanics, 3 (3%) Arabs and 5 (4%) of the Others cohort died from metastasis (Table 4).

A multivariate analysis based on race with 8th edition AJCC pT stage and adjuvant therapy as covariates revealed a statistically significant effect of race on outcomes. Hispanics had a hazard ratio of 6.75 (95% CI, 1.552 to 29.356; $p=0.011$) for orbital tumour recurrence compared to Caucasians. Asians had a hazard ratio of 3.212 (95% CI, 1.135–9.091; $p=0.028$), and Hispanics had a hazard ratio of 3.223 (95% CI, 1.0.72–9.695; $p=0.037$) for metastasis-related death compared to Caucasians (Table 5).

The 10-year Kaplan–Meier recurrence-free survival estimates were 99% for Caucasians, 95% for Asians, 90% for Hispanics and 95% for the Others cohort. The 10-year Kaplan–Meier overall survival estimates were 98% for Caucasians, 90% for Asians, 92% for Hispanics and 95% for the Others cohort for recurrence-free survival (Table 6, Figure 1).

4 | Discussion

While early diagnosis and appropriate treatment are crucial for good outcomes in any cancer, the influence of race on cancer survival as an independent risk factor has been debated for various cancers. While inequitable social, economic, political, behavioural and psychological factors are significant contributors to racial disparities in cancer outcomes [6–9, 16, 17], there are also potential biological mechanisms that may underlie these observed differences.

For example, it has been shown that African Americans, American Indians and Hispanic women are at higher risk of more aggressive subtypes of breast cancer compared to non-Hispanic White women, resulting in a higher risk of cancer-specific mortality [18]. African American men are likely to present with more advanced and aggressive prostate cancer with a 2.3 times higher risk of cancer-specific mortality compared to non-Hispanic White men [19]. Similarly, racial differences have been noted for lung cancer [20], colorectal cancer [21], pancreatic cancer [22], liver cancer [23], gastric cancer [24] and leukaemia [25]. The role of tumour biology is being investigated for racial disparity in tumour behaviour and outcomes for these cancers [9].

In our current study on retinoblastoma, race was an independent risk factor for metastasis-related mortality. Asians and Hispanics had three times higher risk of mortality compared to Caucasians, despite uniform treatment. This could possibly be related to the aggressive infiltrative behaviour of the tumour. In a study comparing 331 Asian Indians and 193 Caucasians who underwent primary enucleation for retinoblastoma, it was noted that Asian Indians had two times higher risk for harbouring high-risk histopathology features compared to Caucasians [26]. Asian Indians had a 5-fold and 3-fold greater risk of optic nerve and massive choroidal invasion, respectively, compared with

TABLE 3 | Analysis of patients with retinoblastoma treated with primary enucleation based on race within 8th edition AJCC cT stages: histopathology features.

	AJCC cT2 $n=572$						AJCC cT3 $n=661$						AJCC cT4 $n=58$					
Feature	**Caucasians $n=120$, n (%)**	**Asians $n=239$, n (%)**	**Hispanics $n=175$, n (%)**	**Arabs $n=18$, n (%)**	**Others $n=19$, n (%)**	**p**	**Caucasians $n=104$, n (%)**	**Asians $n=488$, n (%)**	**Hispanics $n=51$, n (%)**	**Arabs $n=5$, n (%)**	**Others $n=12$, n (%)**	**p***	**Caucasians $n=7$, n (%)**	**Asians $n=51$, n (%)**	**Hispanics $n=0$, n (%)**	**Arabs $n=0$, n (%)**	**Others $n=0$, n (%)**	**p***
Tumour growth pattern																		
Endophytic	41 (38)	144 (65)	97 (61)	1 (6)	2 (11)		41 (42)	227 (49)	21 (46)	(0)	2 (17)		1 (14)	17 (33)	0 (0)	0 (0)	0 (0)	
Exophytic	28 (26)	30 (14)	23 (14)	2 (13)	8 (42)		22 (23)	111 (24)	14 (30)	0 (0)	5 (42)		1 (14)	3 (6)	0 (0)	0 (0)	0 (0)	
Mixed endopthytic-exophytic	38 (36)	44 (20)	38 (24)	13 (81)	9 (47)		27 (28)	114 (25)	9 (20)	4 (80)	5 (42)		4 (57)	31 (61)	0 (0)	0 (0)	0 (0)	
Diffuse infiltrating	0 (0)	5 (2)	1 (<1)	0 (0)	0 (0)	<0.001	7 (7)	10 (2)	2 (4)	0 (0)	0 (0)	0.008	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0.034
Tumour differentiation																		
Well-differentiated	18 (17)	51 (22)	11 (7)	8 (50)	9 (26)		11 (11)	82 (18)	3 (6)	3 (60)	1 (8)		1 (14)	2 (4)	0 (0)	0 (0)	0 (0)	
Moderately differentiated	39 (36)	118 (52)	73 (45)	5 (31)	8 (23)		25 (26)	146 (32)	21 (44)	1 (20)	3 (23)		4 (57)	43 (84)	0 (0)	0 (0)	0 (0)	
Poorly differentiated	33 (31)	48 (21)	70 (44)	3 (19)	17 (49)		24 (25)	194 (42)	19 (40)	0 (0)	9 (70)		1 (14)	5 (10)	0 (0)	0 (0)	0 (0)	
Undifferentiated	18 (17)	11 (5)	7 (4)	0 (0)	1 (3)	<0.001	37 (38)	39 (8)	5 (10)	0 (0)	0 (0)	<0.001	1 (14)	1 (2)	0 (0)	0 (0)	0 (0)	0.198
Tumour infiltration																		
Aqueous seeds	0 (0)	6 (2)	18 (10)	1 (5)	(0)	<0.001	20 (19)	75 (15)	21 (41)	0 (0)	2 (15)	<0.001	3 (43)	14 (28)	0 (0)	0 (0)	0 (0)	0.671
Iris	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0.379	10 (10)	56 (12)	9 (18)	0 (0)	1 (8)	0.543	2 (29)	14 (28)	0 (0)	0 (0)	0 (0)	0.950
Trabecular meshwork	2 (2)	2 (1)	0 (0)	1 (5)	(0)	0.146	7 (7)	31 (6)	6 (12)	0 (0)	1 (8)	0.642	2 (29)	3 (6)	0 (0)	0 (0)	0 (0)	0.045
Schlemm's canal	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0.592	3 (3)	20 (4)	2 (4)	0 (0)	0 (0)	0.898	2 (29)	3 (6)	0 (0)	0 (0)	0 (0)	0.045
Ciliary body	1 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0.774	9 (9)	47 (10)	17 (33)	0 (0)	3 (23)	<0.001	2 (29)	3 (6)	0 (0)	0 (0)	0 (0)	0.045
Choroid	46 (38)	69 (29)	93 (53)	5 (26)	6 (32)	<0.001	62 (60)	234 (48)	33 (65)	3 (60)	9 (69)	0.032	5 (71)	37 (72)	0 (0)	0 (0)	0 (0)	0.950
Minor	30 (25)	28 (12)	52 (30)	4 (21)	4 (21)	<0.001	47 (45)	81 (17)	15 (29)	1 (20)	3 (23)	<0.001	2 (29)	1 (2)	0 (0)	0 (0)	0 (0)	0.003
Massive	16 (13)	41 (17)	41 (23)	1 (5)	2 (11)	0.082	15 (14)	153 (31)	28 (35)	2 (40)	6 (46)	0.005	3 (43)	36 (71)	0 (0)	0 (0)	0 (0)	0.143
Optic nerve	62 (52)	140 (59)	125 (71)	5 (26)	13 (68)	0.001	88 (85)	331 (68)	36 (71)	2 (40)	12 (92)	0.002	6 (86)	50 (51)	0 (0)	0 (0)	0 (0)	0.094
Prelaminar	40 (41)	40 (29)	45 (47)	3 (18)	9 (60)	0.005	47 (75)	88 (36)	9 (38)	1 (20)	2 (67)	<0.001	0 (0)	50 (2)	0 (0)	0 (0)	0 (0)	0.386
Laminar	14 (12)	42 (23)	29 (23)	0 (0)	1 (6)	0.015	21 (25)	81 (25)	11 (310	1 (20)	0 (0)	0.767	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0.505
Post-laminar	5 (4)	55 (23)	35 (22)	2 (10)	2 (11)	<0.001	17 (17)	139 (30)	10 (22)	0 (0)	8 (50)	<0.001	4 (80)	30 (91)	0 (0)	0 (0)	0 (0)	0.459

(Continues)

TABLE 3 | (Continued)

Feature	AJCC cT2 *n* = 572						AJCC cT3 *n* = 661						AJCC cT4 *n* = 58					
	Caucasians *n* = 120, *n* (%)	Asians *n* = 239, *n* (%)	Hispanics *n* = 175, *n* (%)	Arabs *n* = 18, *n* (%)	Others *n* = 19, *n* (%)	*p*	Caucasians *n* = 104, *n* (%)	Asians *n* = 488, *n* (%)	Hispanics *n* = 51, *n* (%)	Arabs *n* = 5, *n* (%)	Others *n* = 12, *n* (%)	*p**	Caucasians *n* = 7, *n* (%)	Asians *n* = 51, *n* (%)	Hispanics *n* = 0, *n* (%)	Arabs *n* = 0, *n* (%)	Others *n* = 0, *n* (%)	*p**
Optic nerve transection	3 (3)	3 (1)	16 (9)	0 (0)	1 (5)	< 0.001	3 (3)	23 (5)	6 (12)	0 (0)	2 (15)	0.063	2 (29)	18 (35)	0 (0)	0 (0)	0 (0)	0.726
Combined prelaminar/ laminar optic nerve and minor choroid	32 (27)	47 (20)	51 (29)	1 (5)	5 (26)	0.056	49 (47)	105 (22)	17 (33)	3 (60)	5 (39)	< 0.001	2 (29)	2 (4)	0 (0)	0 (0)	0 (0)	0.016
Sclera																		
Partial thickness	1 (1)	4 (2)	7 (4)	0 (0)	0 (0)		5 (5)	27 (6)	7 (0)	0 (0)	1 (8)		0 (0)	2 (6)				
Full thickness	0 (0)	1 (< 1)	0 (0)	0 (0)	0 (0)	0.588	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)	0.378	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	0.692
Extrascleral tissue	0 (0)	0 (0)	3 (2)	1 (5)	0 (0)	0.027	2 (2)	16 (3)	5 (10)	0 (0)	0 (0)	0.110	1 (14)	15 (30)	0 (0)	0 (0)	0 (0)	0.401
8th edition AJCC staging																		
pT1	79 (66)	138 (58)	84 (48)	14 (74)	11 (58)		38 (37)	206 (42)	18 (35)	2 (40)	1 (18)		1 (14)	1 (2)	0 (0)	0 (0)	0 (0)	
pT2a	19 (16)	13 (5)	24 (14)	1 (5)	4 (21)		29 (28)	31 (6)	6 (12)	1 (20)	0 (0)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
pT2b	1 (1)	0 (0)	0 (0)	1 (5)	0 (0)		6 (6)	18 (4)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
pT3a	12 (10)	27 (11)	15 (9)	0 (0)	1 (5)		9 (9)	59 (12)	0 (0)	2 (40)	2 (15)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
pT3b	5 (4)	53 (22)	32 (18)	2 (10)	2 (10)		13 (12)	113 (23)	9 (18)	0 (0)	7 (54)		4 (57)	18 (35)	0 (0)	0 (0)	0 (0)	
pT3c	1 (< 1)	4 (2)	3 (2)	0 (0)	0 (0)		5 (5)	26 (5)	5 (10)	0 (0)	1 (8)		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	
pT3d	0 (0)	1 (< 1)	0 (0)	0 (0)	0 (0)		0 (0)	4 (1)	0 (0)	0 (0)	0 (0)		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	
pT4	3 (2)	3 (1)	17 (8)	1 (5)	1 (5)	< 0.001	4 (4)	31 (6)	7 (14)	0 (0)	2 (15)	< 0.001	2 (29)	29 (57)	0 (0)	0 (0)	0 (0)	0.306

Abbreviation: AJCC = American Joint Committee on Cancer.

TABLE 4 | Analysis of 1426 patients with retinoblastoma treated with primary enucleation based on race: treatment and outcomes.

Feature	Caucasians $n=231$, n (%)	Asians $n=841$, n (%)	Hispanics $n=226$, n (%)	Arabs $n=96$, n (%)	Others $n=32$, n (%)	p
Adjuvant treatment						
None	139 (60)	342 (41)	111 (49)	57 (59)	15 (47)	
IVC	81 (35)	479 (57)	90 (40)	38 (40)	17 (53)	
IVC + EBRT	11 (5)	20 (2)	25 (11)	1 (1)	0 (0)	<0.001[a]
Number of cycles of chemotherapy						
Mean (median, range)	5 (4, 2–6)	6 (6, 1–12)	6 (6, 2–11)	7 (8, 2 to 8)	6 (6, 6–6)	<0.001[h,b]
EBRT dose (Gy)						
Mean (median, range)	50 (50, 50)	41 (40, 40–50)	43 (45, 30–50)	45 (45, 45–45)	na	<0.001[h,c]
Outcomes						
Orbital tumour recurrence	2 (1)	36 (4)	20 (9)	0 (0)	2 (6)	<0.001[d]
Interval between enucleation and orbital tumour recurrence (months)	2 (3, 3–4)	11 (8, <1–36)	11 (9, 1–42)	na	46 (46, 9–83)	<0.001[h,e]
Metastasis-related death	5 (2)	110 (13)	28 (12)	3 (3)	2 (6)	<0.001[f]
Interval between enucleation and death (months)	9 (9, 6–12)	14 (11, <1–72)	12 (11, 3–26)		12 (11, 10–16)	0.961[h]
Follow-up duration (months)						
Mean (median, range)	54 (52, <1–134	34 (28, <1–149)	53 (50, <1–138)	44 (40, <1–137)	48 (46, 1–123)	<0.001[i,g]

Abbreviations: EBRT = external beam radiotherapy; IVC = intravenous chemotherapy.
[a]Post hoc analysis showed that adjuvant IVC administration was significantly different between Caucasians vs. Asians; IVC + EBRT administration was different between Asians vs. Hispanics and Hispanics vs. Arabs.
[b]Post hoc analysis showed that Caucasians were significantly different from Asians, Hispanics and Others; Asians were different from Others; Hispanics were different from Others.
[c]Post hoc analysis showed that Caucasians were significantly different from Hispanics.
[d]Post hoc analysis showed that Hispanics were significantly different from Caucasians and Arabs.
[e]Post hoc analysis showed that Caucasians were significantly different from Asians and Hispanics.
[f]Post hoc analysis showed that Caucasians were significantly different from Asians and Hispanics; Asians were significantly different from Arabs; Hispanics were different from Others.
[g]Post hoc analysis showed that Asians were significantly different from Caucasians, Hispanics, Caucasians were different from Others.
[h]Kruskal Wallis.
[i]ANOVA.

TABLE 5 | Analysis of 1426 patients with retinoblastoma treated with primary enucleation based on race: Cox proportional hazards analysis of outcomes.

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	***p***	**Hazard ratio (95% confidence interval)**	***p***
Orbital tumour recurrence				
Race				
Caucasian	Reference			
Asian	4.882 (1.170–20.366)	0.03	4.098 (0.946–17.758)	0.059
Hispanic	9.001 (2.104–38.513)	0.003	6.820 (1.568–29.660)	0.010
Arab	0.000 (0.000 to 1.649E + 190)	0.963	0.000 (0.000 to 1.193E + 290)	0.974
Others	6.650 (0.937–47.212)	0.058	2.282 (0.305–17.061)	0.422
8th edition AJCC pT stage				
pT1	Reference			< 0.001
pT2a	2.383 (0.799–7.112)	0.119	5.226 (1.700–16.066)	0.004
pT2b	0 (0 to 5.224E + 269)	0.974	0.000 (0 to 1.737E + 268)	0.990
pT3a	0.512 (0.065–4.039)	0.525	2.235 (0.268–18.2653)	0.458
pT3b	3.163 (1.332–7.511)	0.009	13.894 (5.039–38.312)	< 0.001
pT3c	8.835 (3.142–24.841)	< 0.001	41.156 (12.774–132.598)	< 0.001
pT3d	26.19 (5.651–121.389)	< 0.001	135.171 (25.084–728.399)	< 0.001
pT4	22.791 (10.471–49.604)	< 0.001	85.680 (33.925–216.390)	< 0.001
Adjuvant therapy				
Received adjuvant therapy	Reference			
No adjuvant therapy	0.792 (0.466–1.345)	0.388	6.532 (3.310 to 12.891)	< 0.001
Metastasis-related death				
Race		0.067		
Caucasian	Reference			
Asian	4.126 (1.493–11.401)	0.006	3.210 (1.135–9.083)	0.028
Hispanic	3.968 (1.334–11.792)	0.013	3.217 (1.070–9.675)	0.038
Arab	1.956 (0.438–8.739	0.380	1.801 (0.398–8.145)	0.445
Others	3.464 (0.634–18.913)	0.151	1.001 (0.174–5.745)	0.999
8th edition AJCC pT stage				
pT1	Reference			
pT2a	2.826 (0.797–10.014)	0.108	6.350 (1.734–23.136)	0.005
pT2b	4.355 (0.524–36.177)	0.173	15.690 (1.774–138.801)	0.013
pT3a	5.443 (1.829–16.201)	0.002	19.496 (5.836–65.128)	< 0.001
pT3b	10.723 (4.426–25.982)	< 0.001	38.258 (13.565–107.899)	< 0.001
pT3c	11.871 (3.622–38.906)	< 0.001	44.252 (12.0.21–162.898)	< 0.001
pT3d	24.801 (2.985–206.061)	0.003	92.128 (10.000–814.769)	< 0.001
pT4	49.746 (20.643–119.882)	< 0.001	202.493 (68.656–597.228)	< 0.001

(Continues)

TABLE 5 | (Continued)

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	*p*	Hazard ratio (95% confidence interval)	*p*
Adjuvant therapy				
Yes	Reference			
No	0.338 (0.2–0.571)	< 0.001	5.153 (2.602–10.207)	< 0.001

Abbreviation: AJCC = American Joint Committee on Cancer.

TABLE 6 | Analysis of 1426 patients with retinoblastoma treated with primary enucleation based on race: Kaplan–Meier survival analysis.

	Caucasians	Asians	Hispanics	Arabs*	Others
	Survival estimate ± SE	Survival estimate ± SE	Survival estimate ± SE	Survival estimate ± SE	Survival estimate ± SE
Recurrence free survival					
1 years	99.5 ± 0.5	96.3 ± 0.7	93.6 ± 1.7	100	96.4 ± 3.5
3 years	98.9 ± 0.7	94.7 ± 0.9	91.0 ± 1.9	100	96.4 ± 3.5
5 years	98.9 ± 0.7	94.7 ± 0.9	90.3 ± 2.1	100	96.4 ± 3.5
10 years	98.9 ± 0.7	94.7 ± 0.9	90.3 ± 2.1	100	84.4 ± 11.7
Overall survival					
1 years	97.8 ± 1.1	94.6 ± 0.9	95.2 ± 1.5	97.1 ± 2.0	92.6 ± 5.0
3 years	97.8 ± 1.1	92.1 ± 1.1	91.6 ± 2.0	95.5 ± 2.5	92.6 ± 5.0
5 years	97.8 ± 1.1	90.9 ± 1.3	91.6 ± 2.0	95.5 ± 2.5	92.6 ± 5.0
10 years	97.8 ± 1.1	89.9 ± 1.6	91.6 ± 2.0	95.5 ± 2.5	92.6 ± 5.0

Abbreviation: SE = standard error.
*No recurrences.

Caucasians [26]. In the current study, the risk of post-laminar optic nerve infiltration and massive choroidal invasion was higher in Asians and Hispanics compared to Caucasians despite uniform AJCC clinical staging at the time of enucleation.

A difference in the biological behaviour of retinoblastoma has been demonstrated in animal models using different cell lines [27]. Retinoblastoma that develops from Y79 human retinoblastoma cells (originally from Yale University School of Medicine, New Haven, USA) derived from a 2.5-year-old Caucasian girl with a strong maternal family history of retinoblastoma exhibits aggressive behaviour with rapidly growing tumour and high metastatic potential, while retinoblastoma that develops from WERI-Rb cell line (originally from Wills Eye Hospital, Philadelphia, USA) derived from a 1-year-old Caucasian girl with no family history of retinoblastoma behaves as a localised tumour with low metastatic potential [27–29]. This difference in cell lines might relate to tumour behavioural differences in disparate populations, though both cell lines originated from Caucasians. This warrants a focused study on the biological behaviour and genetic makeup of retinoblastoma in different populations.

High-risk histopathology features of retinoblastoma warrant adjuvant treatment to lower the risk of metastasis-related mortality. Various studies have shown that adjuvant treatment minimises the risk of metastasis and improves survival [26, 30, 31]. In the current study, multivariate analysis showed that adjuvant chemotherapy protects against orbital tumour recurrence and metastasis-related mortality. However, race was a risk factor for metastasis-related mortality in Asians and Hispanics, with a 3-fold greater risk compared to Caucasians, independent of pathological T stage and adjuvant treatment. These findings underscore the importance of stringent follow-up and a more aggressive treatment approach when needed in Asians and Hispanics who manifest high-risk histopathological features.

The strength of this study lies in its inclusion of a diverse cohort of patients from different racial backgrounds, enabling a comparative analysis based on race. This comprehensive approach provides a more nuanced understanding of how race might influence outcomes in retinoblastoma. Notably, this is the first study to explore the influence of race on the pathology and outcomes of retinoblastoma, marking a significant step forward in understanding and addressing racial disparities in this particular cancer.

The study's limitations include its retrospective nature, which may introduce biases related to data collection, including

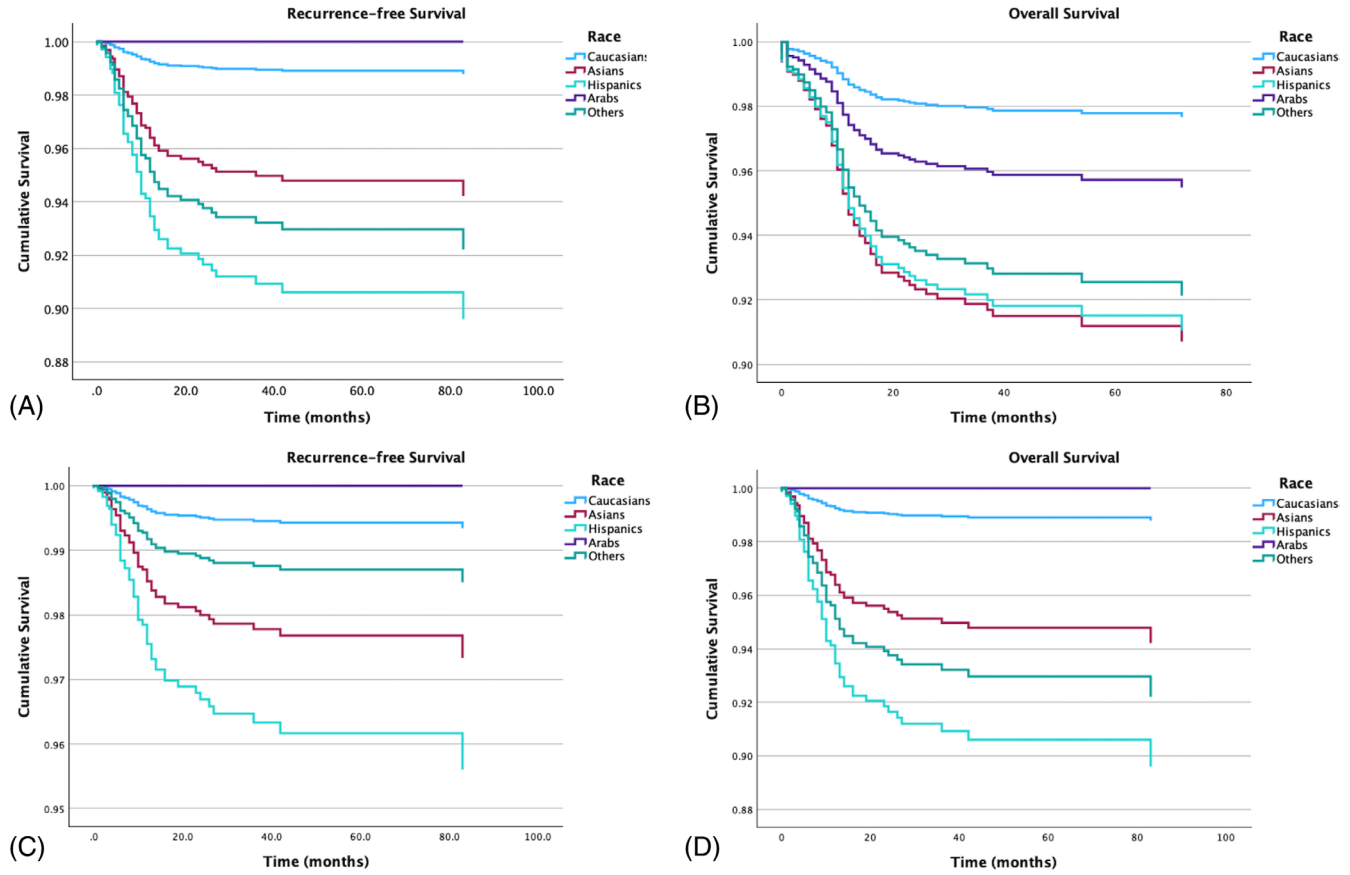

FIGURE 1 | Kaplan–Meier survival curves for recurrence-free survival and overall survival based on race (A and B) alone and based on race, taking into consideration the 8th edition pT stage and adjuvant therapy (C and D).

heterogeneity, pathological reporting to a limited extent and analysis. Additionally, the study lacks detailed information on the genetic or molecular differences in tumour biology, which limits the ability to fully understand the underlying biological mechanisms contributing to the observed racial disparities in retinoblastoma outcomes. The role of certain confounders, such as delay in access to care and its influence on tumour pathology, was beyond the scope of this study. Additionally, the number of patients of Arab, African American, African and Indigenous Australian populations was limited. Lastly, adequate information from the African cohort is lacking as no RB treatment centres from Africa volunteered to participate in the study.

In conclusion, race influences the biological behaviour of retinoblastoma, with an increased propensity for massive choroidal infiltration and post-laminar optic nerve invasion in Asians and Hispanics compared to Caucasians. Additionally, evidence from this current study suggests that race is an independent predictor of outcomes in retinoblastoma, including orbital tumour recurrence and metastasis-related death, beyond pathological T stage and adjuvant treatment. Further prospective research analysing the clinical, pathological and advanced molecular studies against outcomes in different races is needed for a more comprehensive understanding of the influence of race on retinoblastoma outcomes.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Appendix

High-Risk Retinoblastoma Collaborative Group (In Alphabetical Order)

Alia Ahmad (University of Children Health Sciences, Children's Hospital, Lahore, Pakistan), Kavya Madhuri Bejjanki (LV Prasad Eye Institute, Vijayawada, India), Rosdali Diaz-Coronado (Pediatric Oncology Department, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Universidad Peruana Cayetano Heredia, Lima, Peru), Maya Eiger-Moscovich (Hadassah Medical Center, Jerusalem, Israel), James E. Elder (Department of Ophthalmology, Royal Children's Hospital, Victoria, Australia; University of Melbourne, Melbourne, Australia), Ido Didi Fabian (Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel), Shahar Frenkel (Hadassah Medical Center, Jerusalem, Israel), Hans Grossniklaus (Emory University School of Medicine, Georgia, USA), G. Baker Hubbard III (Emory University School of Medicine, Georgia, USA), Swathi Kaliki (The Operation Eyesight Universal Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India), Anasua Ganguly Kapoor (LV Prasad Eye Institute, Vijayawada, India), Mona Mohammad (King Hussein Cancer Center, Amman, Jordan), John D. McKenzie (Department of Ophthalmology, Royal Children's Hospital, Victoria, Australia), Jacob Pe'er (Hadassah Medical Center, Jerusalem, Israel), Suryasnata Rath (LV Prasad Eye Institute, Bhubaneswar, India), M. Ashwin Reddy (Royal London Hospital, Barts Health NHS Trust, London, UK), Olivia Rolfe (Department of Ophthalmology, Royal Children's Hospital, Victoria, Australia), Soma Rani Roy (Chittagong Eye Infirmary and Training Complex, Chittagong, Bangladesh), Mandeep S. Sagoo (Royal London Hospital, Barts Health NHS Trust, London, UK; Moorfields Eye Hospital NHS Foundation Trust, London, UK), Carol L. Shields (Ocular Oncology Service, Wills Eye Hospital, Philadelphia, USA), Sandra E. Staffieri (Department of Ophthalmology, Royal Children's Hospital, Victoria, Australia; University of Melbourne, Melbourne, Australia; Murdoch Children's Research Institute, Melbourne, Australia; Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia), Mika Tanabe (Kyushu University, Fukuoka, Japan), Ushakova Tatiana (Department of Surgical Methods of Treatment with chemotherapy No. 1 (Head and Neck Tumors), N. N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation; L.A. Durnov Department of Pediatric Oncology of the Russian Medical Academy of Continuing Professional Education, Moscow, Russian Federation) Devjyoti

Tripathy (LV Prasad Eye Institute, Bhubaneswar, India), Vicktoria Vishnevskia-Dai (Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel), Vijitha S. Vempuluru (The Operation Eyesight Universal Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India), Polyakov Vladimir (Department of Surgical Methods of Treatment with chemotherapy No. 1 (Head and Neck Tumors), N. N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation; L.A. Durnov Department of Pediatric Oncology of the Russian Medical Academy of Continuing Professional Education, Moscow, Russian Federation; Department of ENT Diseases of the Faculty of Pediatrics of the Federal State Educational Institution of Higher Education of N.I. Pirogov Russian National Research Medical University, Moscow, Russian Federation), Yacoub A Yousef (King Hussein Cancer Center, Amman, Jordan).