

Global retinoblastoma survival and globe preservation: a systematic review and meta-analysis of associations with socioeconomic and health-care factors

Emily S Wong*, Richard W Choy*, Yuzhou Zhang, Wai Kit Chu, Li Jia Chen, Chi Pui Pang, Jason C Yam



Summary

Background Despite advancements in globe-preserving treatments, improvements in retinoblastoma outcomes are inconsistent across income levels and geographical locations. We aimed to investigate trends in global retinoblastoma survival and globe preservation during the past 40 years. We also examined associated socioeconomic and health-care factors and global survival disparity.

Methods We did a systematic review and meta-analysis by screening articles in any language in nine databases (PubMed, Embase, ScienceDirect, Web of Science, OpenGrey, Global Burden of Disease, Global Health Data Exchange, Global Index Medicus, and International Agency for the Prevention of Blindness) published between Jan 1, 1981, and Oct 8, 2021. We screened for articles that described retinoblastoma overall survival or globe salvage, or both. All reported studies were subsequently stratified into four periods: 1980–89, 1990–99, 2000–09, and 2010–20. Indicators on socioeconomic and health-care factors were extracted from the World Bank and WHO. Ophthalmology-related indicators were further parsed from the International Agency for the Prevention of Blindness. Between-study heterogeneities by income level were assessed by mixed-effect meta-analysis. Associations of retinoblastoma outcome with socioeconomic and health-care factors and factors for survival prediction were investigated by multivariable linear regressions. This study is registered with PROSPERO, number CRD42020221556.

Findings Our search identified 14 621 articles, of which 314 studies were included for analysis after screening, including 38 130 patients from 80 regions globally presenting during 1980–2020. 255 articles were entered for time-trend meta-analysis, covering 29 106 patients from 73 countries. Both overall survival (from 79% [95% CI 74–84] to 88% [83–93]; $p=0.017$) and globe salvage rate (from 22% [14–32] to 44% [36–52]; $p=0.0003$) improved significantly over the four decades. Wide disparities were observed between higher-income and lower-income countries. Overall survival, globe salvage, and globe salvage for advanced intraocular disease correlated positively with income level. Higher overall survival was associated with lower Gini index ($p=0.0001$) and with populations that had smaller percentages living in rural areas ($p=0.0005$). Higher globe salvage was associated with better health-care financing and accessibility ($p=0.030$). Overall survival ($p=0.0024$) and globe salvage ($p=0.022$) were both associated positively with education level. Survival gaps were observed in sub-Saharan Africa and southeast and southwest Asia.

Interpretation Retinoblastoma treatment outcomes have improved globally over the past four decades but large disparities persist between higher-income and lower-income countries, with some areas having major survival gaps. Targeted health-care policy making with increased health-care financing and accessibility are needed in low-income and lower-middle-income countries to improve retinoblastoma outcomes worldwide.

Funding Health and Medical Research Fund (Hong Kong) and Children Cancer's Foundation (Hong Kong).

Copyright © 2022 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Retinoblastoma is the most common intraocular childhood cancer and is treatable, especially when detected early.¹ Enucleation remains an important treatment that highly reduces mortality, particularly in group D and E patients, according to the International Intraocular Retinoblastoma Classification (IIRC) or Intraocular Classification of Retinoblastoma (ICRB) schemes.^{2,3} However, enucleation leads to total vision loss and severely impairs quality of life.⁴ Over the years, various globe salvage strategies (defined as free from enucleation or

exenteration treatment), such as intra-arterial chemotherapy, intravenous chemotherapy (chemoreduction), and plaque radiotherapy, have been developed as alternatives to enucleation for management of advanced intraocular disease.⁵ The expanding set of treatment options against retinoblastoma has greatly improved overall survival and globe preservation.^{5,6}

Despite these breakthroughs, early detection is the most important prerequisite for better outcomes. However, the capability for early diagnosis is affected by socioeconomic factors and is a major challenge,

Lancet Glob Health 2022; 10: e380–89

Published Online
January 27, 2022
[https://doi.org/10.1016/S2214-109X\(21\)00555-6](https://doi.org/10.1016/S2214-109X(21)00555-6)

This online publication has been corrected. The corrected version first appeared at [thelancet.com/lancetgh](https://www.thelancet.com/lancetgh) on November 20, 2024

See [Comment](#) page e307

*Joint first authors and contributed equally

Department of Ophthalmology and Visual Sciences (E S Wong FCOphth, R W Choy MSc, Y Zhang MSc, W K Chu DPhil, L J Chen FCOphth, Prof C P Pang DPhil, J C Yam FCOphth) and Hong Kong Hub of Paediatric Excellence (W K Chu, L J Chen, Prof C P Pang, J C Yam), The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; Department of Ophthalmology, Hong Kong Children's Hospital, Hong Kong Special Administrative Region, China (E S Wong, J C Yam); Hong Kong Eye Hospital, Hong Kong Special Administrative Region, China (E S Wong, J C Yam); Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong Special Administrative Region, China (L J Chen, J C Yam)

Correspondence to:
Dr Jason C Yam, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, Hong Kong Special Administrative Region, China yamcheuksing@cuhk.edu.hk

Research in context

Evidence before this study

We searched nine databases (PubMed, Embase, ScienceDirect, Web of Science, OpenGrey, Global Burden of Disease, Global Health Data Exchange, Global Index Medicus, and International Agency for the Prevention of Blindness) for primary research articles published between Jan 1, 1980, and Oct 8, 2021. The search included grey literature and was repeated using individual country names, together with the key terms “retinoblastoma” AND (“outcome” OR “prognosis” OR “survival” OR “salvage” OR “enucleation” OR “prevalence” OR “incidence”). No restrictions were imposed on language of publication; age, sex, or ethnicity of participants; setting of diagnosis and treatment; or duration of follow-up. We identified one study from 2020, which focused on the association between retinoblastoma presentation and national income level, and one from 2010, which focused on the association between retinoblastoma survival and human development index. These studies showed that lower-income locations are more susceptible to advanced retinoblastoma presentation, in terms of both age at presentation and disease stage, and have poorer survival rates than higher-income areas. Socioeconomic status and health-care infrastructure were also strongly associated with retinoblastoma survival. Yet the effects of socioeconomic factors and ophthalmology service availability on retinoblastoma prognosis were not explored. The disparities in overall and stage-specific globe salvage rates were not investigated. During the past decade, new globe salvage techniques have resulted in improved treatment outcomes, but access to these technologies varies widely across countries and income levels.

Added value of this study

To improve global retinoblastoma treatment outcomes via targeted policy development, it is important to identify the upstream socioeconomic factors that might influence disease outcomes and disparity among countries with different income

levels. Our study is the first meta-analysis covering the global trends and patterns in retinoblastoma survival and globe preservation during the past 40 years. 38 130 patients from 80 regions globally presenting during 1980–2020 were included. We showed that, even though overall survival and globe salvage have improved significantly during the past four decades, there is a large outcome disparity between high-income and low-income countries, with survival gaps observed in sub-Saharan Africa and southeast and southwest Asia. Overall survival, globe salvage rate, and advanced intraocular stage globe salvage rate also correlate positively with income levels. Finally, we identified the socioeconomic factors that were associated with improved outcomes. Overall survival was positively associated with populations that had smaller percentages living in rural areas and with lower Gini index. Higher globe salvage rate was associated with better health-care financing and accessibility. Both were associated positively with education level. We have also highlighted the ongoing efforts to improve retinoblastoma outcomes worldwide.

Implications of all the available evidence

Our meta-analysis highlights the global disparity between high-income and low-income countries in terms of retinoblastoma survival and globe salvage rate, and identifies socioeconomic risk factors associated with both. This information will be useful to raise awareness among policy makers and non-governmental organisations as well as to guide resource allocation for retinoblastoma treatment on both a local and international level. As retinoblastoma is the commonest intraocular malignancy in children and is a readily treatable tumour as long as early detection and prompt initiation of treatment is accessible, this study has important implications for improving the treatment outcomes and long-term survival for children with this condition around the world.

particularly in lower-income countries.^{7,8} In addition, although globe salvage technologies have become widely available, access to such technologies and to health care more generally varies enormously across countries, as indicated in a previous global cross-sectional study.⁷ Late disease detection, suboptimal socioeconomic status, and poor health-care system performance are associated with poor survival rates.^{7,8}

To improve global retinoblastoma treatment outcomes, robust data are needed as a reference for health authorities to use for targeted policy development. It is important to identify upstream socioeconomic factors that influence disease outcomes and disparity among countries with different income levels. This study aims to adopt an ecological approach to investigate trends and patterns in global retinoblastoma survival and globe preservation over the past 40 years. We also examine their associations with socioeconomic and health-care

factors and estimate global survival disparity in the past decade.

Methods

Search strategy and eligibility criteria

We did a systematic review and meta-analysis to assess for reported overall survival and globe salvage rates for retinoblastoma globally and its associated socioeconomic and health-care factors. Procedures of the current study followed the PRISMA guidelines. We searched four databases (PubMed, ScienceDirect, Embase, and Web of Science) for studies published between Jan 1, 1981, and Oct 8, 2021, which reported on retinoblastoma survival and globe salvage status. The search was repeated using individual country names, together with the key terms “retinoblastoma” AND (“outcome” OR “prognosis” OR “survival” OR “salvage” OR “enucleation” OR “prevalence” OR “incidence”; appendix pp 21–22).

See Online for appendix

We identified additional studies by searching the reference list of included studies. On the basis of the guidelines by the Canadian Agency for Drugs and Technologies in Health,⁹ relevant grey literature in five databases were searched (OpenGrey, Global Burden of Disease, Global Health Data Exchange, Global Index Medicus, and International Agency for the Prevention of Blindness). No restrictions were imposed on language of publication; age, sex, or ethnicity of participants; setting of diagnosis and treatment; or duration of follow-up. For inclusion in the meta-analysis, studies must have reported summary rates on either retinoblastoma overall survival or globe salvage, or both. Studies that were duplicates, case reports, and outside of the study period; reports of all cancers without a focus on retinoblastoma; and reports on surgical technique or pathological descriptions were excluded. When one study appeared in multiple articles, the article describing the longest follow-up was retained.

RWC and ESW reviewed all of the searched studies using a two-step selection process—ie, title or abstract screening followed by full-text evaluation—to confirm eligibility. The quality of individual studies was evaluated independently by RWC and YZ, with any disagreements resolved through discussion and consensus. The review protocol published by the Joanna Briggs Institute was adopted and the studies were classified into quality categories from low to high.

Data collection

ESW and RWC independently extracted data from each eligible article into a customised database. Extracted data included title, author names, publication year, study design, number of patients, number of eyes treated, average age at presentation, sex and ethnicity of participants, country, staging system used, 5-year survival rate, overall globe salvage rate, and stage-specific globe salvage rate. Studies adopted different staging systems, including the American Joint Committee on Cancer TNM system, the Reese-Ellsworth system, and international systems (IIRC or ICRB). When duplicate data were available from multiple studies, data were extracted from those reports with the most comprehensive reporting or the longest follow-up. When data on multiple cohorts were presented in a single article, each cohort was independently eligible for inclusion. All reported studies were subsequently stratified into four periods: period 1 from 1980 to 1989; period 2 from 1990 to 1999; period 3 from 2000 to 2009; and period 4 from 2010 to 2020.

Socioeconomic and health-care data

Indicators on socioeconomic and health-care factors were extracted to assess their associations with retinoblastoma survival and globe salvage rates. Data on these factors were extracted from the World Bank and WHO in six major domains: demographics, education, general economy, health finance and care accessibility, and

health-care capacity in terms of service delivery and professional workforce. Ophthalmology-related indicators were further parsed from the International Association for Prevention of Blindness. Average values were calculated for the relevant periods during data cleaning. For country income groups, we followed the definitions by the World Bank based on gross national income per capita, and grouped them according to their income level in each decade (appendix p 13).¹⁰

Statistical analysis

For aggregate data, we did a random-effects meta-analysis to describe globe salvage rates for each group according to their respective disease staging system. Inverse-variance weighted point estimates and 95% CIs for globe salvage by classification group were calculated. We looked into the globe salvage of advanced cases of intraocular disease by income level and defined advanced intraocular disease as ICRB or IIRC groups D–E, Reese-Ellsworth stages IV–V, and TNM stages cT2–cT3.

To analyse association patterns among key outcomes and indicators, we did univariable and multivariable linear regressions. Variables were standardised to about $N(0,1)$ before modelling and hence the coefficients correspond to the relative effect size. For multivariable

For ophthalmology-related indicators from the International Association for Prevention of Blindness see <https://www.iapb.org/learn/vision-atlas/>

For appraisal tools by the Joanna Briggs Institute see <https://jbi.global/critical-appraisal-tools>

For socioeconomic and health-care data from the World Bank see <https://databank.worldbank.org>

For socioeconomic and health-care data from WHO see <https://www.who.int/data/gho/>

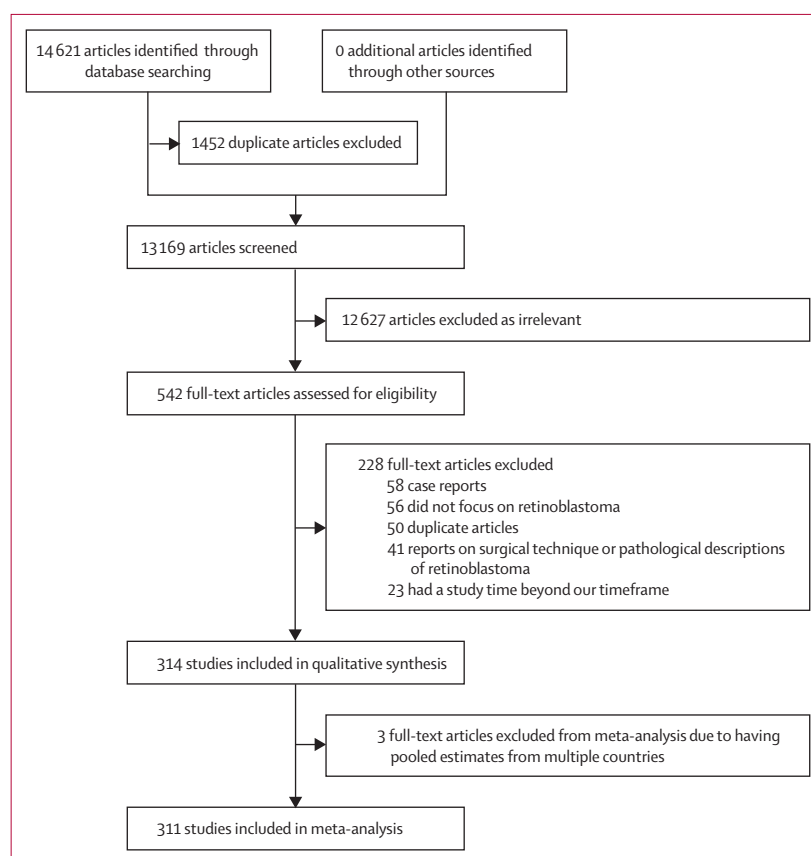


Figure 1: PRISMA diagram for study selection

	Articles, n	Nations, n	Patients, n	Patients with known survival status, n (%)	Patients with known globe salvage status, n (%)	Patients with known globe salvage status and stage, n (%)
Total (by study type, all periods)						
Multicentre pooled estimates	3	30	7035	7035 (100%)	0 (0)	0 (0)
Single-origin estimates	311	80	Not estimated*	Not estimated*	Not estimated*	Not estimated*
Less than 20 years†	255	73	29 106	23 090 (79%)	14 479 (50%)	4246 (15%)
Single-origin study, period 1 (1980–89)						
Total	49	30	4693	4560 (97%)	657 (14%)	0 (0)
Not available	3	3	82	82 (100%)	0 (0%)	0 (0)
LIC	5	4	127	47 (37%)	96 (76%)	0 (0)
LMIC	5	4	203	183 (90%)	0 (0)	0 (0)
UMIC	7	3	480	480 (100%)	156 (33%)	0 (0)
HIC	29	16	3801	3768 (99%)	405 (11%)	0 (0)
Single-origin study, period 2 (1990–99)						
Total	61	33	4874	3831 (79%)	2259 (46%)	42 (1%)
LIC	13	7	757	219 (29%)	674 (89%)	26 (3%)
LMIC	7	7	603	603 (100%)	318 (53%)	0 (0)
UMIC	16	7	812	714 (88%)	783 (96%)	16 (2%)
HIC	25	12	2702	2295 (85%)	484 (18%)	0 (0)
Single-origin study, period 3 (2000–09)						
Total	135	51	12 874	9715 (75%)	6266 (49%)	1404 (11%)
LIC	32	12	3192	2469 (77%)	2598 (81%)	467 (15%)
LMIC	35	15	2336	2206 (94%)	547 (23%)	328 (14%)
UMIC	29	9	2554	1264 (49%)	762 (30%)	300 (12%)
HIC	39	15	4792	3776 (79%)	2359 (49%)	309 (6%)
Single-origin study, period 4 (2010–20)						
Total	90	39	6665	4984 (75%)	5297 (79%)	2800 (42%)
LIC	12	7	1230	910 (74%)	1189 (97%)	75 (6%)
LMIC	31	12	2755	1983 (72%)	2278 (83%)	1130 (41%)
UMIC	26	12	1859	1368 (74%)	1157 (62%)	1020 (55%)
HIC	21	8	821	723 (88%)	673 (82%)	575 (70%)

Each article can be included in more than one decade if they include several subperiods. LIC=low-income country. LMIC=lower-middle-income country. UMIC=upper-middle-income country. HIC=high-income country. *Number not estimated as this is prone to duplication with those studies spanning less than 20 years; characteristics of these studies would be reported separately in the systematic review. †Articles that spanned less than 20 years or with subperiods.

Table 1: Study characteristics

analysis, results from the best subset models were discussed. To show survival disparity in the most recent decade (2010–20), 40 random forest models were trained in parallel with the imputed datasets to predict survival rate for different locations. We imputed missing data with multiple imputation based on predictive mean matching, after excluding survival records that were missing not at random. We then selected the models with root mean square error values that fell in the IQR. We used the DerSimonian-Laird random-effects models with double arcsine transformation to pool outcome estimates for each period. Between-study heterogeneity was assessed with the I^2 statistic. We did a sensitivity

analysis on a fixed-effects model. The potential for publication bias was assessed by funnel plots and Egger's test (threshold for significance was $p < 0.05$). Analyses were done using the R software (version 4.0.2). This study was registered at PROSPERO, number CRD4202221556. The PROSPERO protocol was updated during the study review process.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our search retrieved 14621 articles. We acquired the full text for 543 studies after deduplication and screening for relevance. 314 articles were included after full-text review (figure 1). The final study sample covered 38130 patients from 80 regions worldwide presenting over four decades (1980–2020).

There was a slight male predominance across all four decades in different income groups, but locations with higher income levels had a sex ratio closer to 1 ($p = 0.0028$; appendix p 1). Higher-income regions had younger ages of disease presentation across the four decades than did lower-income regions (appendix p 2). 38 reports presented disease prevalence: eight reported cases per livebirths and 30 reported cases per population aged 0–14 years. The median prevalence per million children was 4.21 (range 1.00–10.15) in 1980–99 and 4.61 (1.80–7.80) in 2000–20 ($p = 0.35$).

Among the 314 articles included in the analysis, three reported pooled estimates for multiple countries. Two of these focused on Europe (25 countries in five regions),^{11,12} whereas one targeted central America (five countries).¹³ Collectively, these articles covered 7035 patients and primarily reported survival rates. They were included for qualitative review but not for meta-analysis because separate reporting for individual countries was not available. For the remaining 311 articles, 56 spanned at least 20 years and had no subperiods, with a median duration of 27 years (IQR 22–32).^{14–69} These articles were included for analysing the associations of socioeconomic and health-care factors but not for time-trend analysis (overall survival and globe salvage across decades) because subperiod data breakdown was not available (figure 1).^{14–69}

Ultimately, 255 articles were entered for time-trend meta-analysis (table 1; appendix pp 23–42). There were 29106 patients from 73 countries. The subsample covered 4693 patients for 1980–89, 4874 for 1990–99, 12874 for 2000–09, and 6665 for 2010–20 (table 1).

Overall survival was reported in 223 articles and the time trend across decades is visualised in the appendix (p 3). Meta-analysis showed an improving trend in global survival estimates with a narrowing survival gap. The corresponding pooled estimates for survival rate in the

	LIC	LMIC	UMIC	HIC	p value	Period overall
Survival rate						
1980–89	52% (13–89; n=3)	43% (22–65; n=4)	71% (64–78; n=5)	87% (83–92; n=26)	LIC vs LMIC: p=0.77; LMIC vs UMIC: p=0.013; UMIC vs HIC: p=0.0001	79% (74–84; n=38)
1990–99	44% (20–70; n=4)	70% (56–81; n=9)	78% (65–89; n=13)	92% (76–86; n=17)	LIC vs LMIC: p=0.098; LMIC vs UMIC: p=0.23; UMIC vs HIC: p=0.090	80% (75–86; n=43)
2000–09	53% (34–72; n=15)	82% (74–88; n=20)	81% (72–89; n=26)	95% (91–98; n=27)	LIC vs LMIC: p=0.0030; LMIC vs UMIC: p=0.84; UMIC vs HIC: p=0.0015	82% (78–86; n=88)
2010–20	57% (36–77; n=3)	83% (70–93; n=12)	92% (86–97; n=17)	98% (95–100; n=12)	LIC vs LMIC: p=0.18; LMIC vs UMIC: p=0.027; UMIC vs HIC: p=0.041	88% (83–93; n=44)
Overall globe salvage rate						
1980–89	9% (0–45; n=2)	NA	11% (2–25; n=5)	34% (21–49; n=8)	UMIC vs LIC: p=0.014	22% (14–32; n=15)
1990–99	5% (0–13; n=6)	21% (4–46; n=4)	23% (8–44; n=9)	71% (60–81; n=17)	LIC vs LMIC: p=0.12; LMIC vs UMIC: p=0.086; UMIC vs HIC: p=0.0010	37% (26–48; n=36)
2000–09	20% (11–30; n=20)	42% (20–65; n=12)	37% (26–48; n=24)	50% (39–62; n=22)	LIC vs LMIC: p=0.080; LMIC vs UMIC: p=0.072; UMIC vs HIC: p=0.089	36% (30–43; n=78)
2010–20	6% (0–20; n=9)	34% (21–49; n=23)	47% (38–56; n=22)	70% (60–80; n=21)	LIC vs LMIC: p=0.0040; LMIC vs UMIC: p=0.13; UMIC vs HIC: p=0.0010	44% (36–52; n=75)
Globe salvage rate for advanced intraocular stage						
1980–89	NA	NA	NA	NA	NA	NA
1990–99	NA	NA	NA	NA	NA	NA
2000–09	3% (0–9; n=6)	7% (0–18; n=6)	31% (20–43; n=4)	27% (17–38; n=11)	NA	22% (16–28; n=27)
2010–20	NA	28% (9–51; n=5)	42% (33–51; n=8)	57% (42–72; n=4)	NA	43% (35–51; n=22)

Numbers in parentheses are 95% CIs. The number of observations (n) are shown; one study might have more than one observation (eg, separate reporting for several subperiods or several locations). Estimates and CIs were generated by DerSimonian-Laird random-effect model. Income-level comparisons were done with two-sample t tests and the corresponding p values were reported. LIC=low-income country. LMIC=lower-middle-income country. UMIC=upper-middle-income country. HIC=high-income country. NA=not available.

Table 2: Pooled estimates stratified by income level and period

four periods were 79% (95% CI 74–84, $I^2=93\%$) for 1980–89, 80% (75–86, $I^2=95\%$) for 1990–99, 82% (78–86, $I^2=98\%$) for 2000–09, and 88% (83–93, $I^2=98\%$; table 2; appendix p 4) for 2010–20; the change in the pooled estimate of survival rates across the world between periods 1 and 4 was significant ($p=0.017$). Comparing 2000–09 and 2010–20, there was a notable improvement in pooled survival rate for upper-middle-income countries (UMICs; 13%), and mild improvements for the other income groups (1–8%).

Overall globe salvage rate was reported in 200 articles (table 1). Notable improvement in overall globe salvage rate was observed especially for high-income countries (HICs) across the decades, from 34% (95% CI 21–49, $I^2=92\%$) in 1980–89 to 70% (60–80, $I^2=96\%$) in 2010–20 ($p=0.0003$; table 2; appendix p 3); the change in the pooled estimate of globe salvage rates across the world between periods 1 and 4 was significant ($p=0.0003$). Less significant improvement was seen for LMICs, and overall globe salvage rate dropped for LICs, from 20% (11–30, $I^2=98\%$) in 2000–09 to 6% (0–20, $I^2=98\%$) in 2010–20. However, this observation was linked to the migration of countries with relatively higher globe salvage rates (ie, India, Pakistan, and Sudan) from LIC to LMIC in 2010–20 (appendix p 5). The pooled estimate in 2010–20 was 6% (0–20, $I^2=98\%$) for LICs, 34% (21–49, $I^2=99\%$) for LMICs, 47% (38–56, $I^2=96\%$) for UMICs, and 70% (60–80, $I^2=96\%$) for HICs (table 2; appendix p 8). Globally, the pooled estimate improved significantly, from 22% [14–32] in 1980–89 to 44% [36–52] in 2010–20 ($p=0.017$).

Subgroup analysis was done by stratifying globe salvage rate by stage. Reporting coverage was low in 1980–2009 (0–11%) but improved notably to 42% in 2010–20 (table 1). For staging system, the ICRB system

was the most commonly used ($n=37$), followed by the Reese-Ellsworth ($n=15$) and IIRC ($n=14$) systems. The pooled globe salvage rates according to the ICRB or IIRC systems were 99% (95% CI 95–100) for group A, 94% (86–99) for group B, 81% (67–92) for group C, 43% (33–54) for group D, and 9% (3–18) for group E (figure 2A). The pooled globe salvage rates according to the Reese-Ellsworth system were 74% (35–98) for stage I, 71% (33–97) for stage II, 57% (22–88) for stage III, 39% (11–73) for stage IV, and 33% (13–58) for stage V (figure 2A). The globe salvage rates of advanced intraocular stage retinoblastoma were pooled and stratified by income level. Higher globe salvage rates for advanced intraocular disease were associated with higher income level, with UMICs improving from 31% (20–43) in 2000–09 to 42% (33–51) in 2010–20 and HICs improving from 27% (17–38) in 2000–09 to 57% (42–72; table 2) in 2010–20. Sparse data were available in LICs and a widening disparity is seen compared with LMICs. From 2000–09 to 2010–20, the rate for LMICs increased from 7% (0–18) to 28% (9–51; figure 2B).

For the sensitivity analysis, pooled estimates from random-effects and fixed-effects models were compared for discrepancies. Results were generally similar, with occasional discrepancies when the number of articles in a stratum was small (appendix pp 4 and 8). Neither funnel plots nor Egger's test results (p values of 0.081–0.78) showed evidence of publication bias (appendix pp 9–10).

Heterogeneity was notable after stratification by income levels (appendix pp 4 and 8). Overall survival was associated with most socioeconomic and health-care factors in the univariate analysis. Factors that showed a strong effect size were completion rates for lower

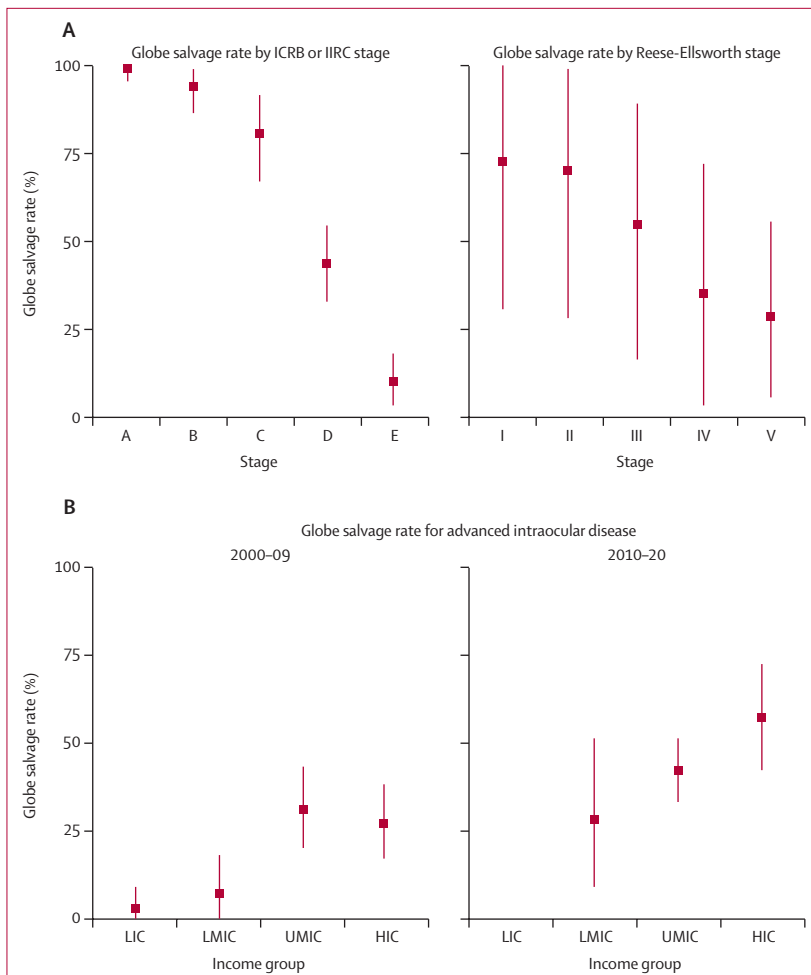


Figure 2: Stage-specific globe salvage rate stratified by staging system and income level

(A) Globe salvage rates decrease with advancing stage of disease using either the ICRB, IIRC, or Reese-Ellsworth classification systems. (B) Advanced intraocular stage globe salvage rate by decade is shown, with higher global salvage rates associated with higher income level. In 2010–20, sparse data were available in LICs and there is a widening disparity when comparing LMICs with UMICs and HICs. Advanced intraocular disease was defined as ICRB or IIRC groups D–E, Reese-Ellsworth stages IV–V, and TNM stages cT2–cT3. HIC=high-income country. ICRB=Intraocular Classification of Retinoblastoma. IIRC=International Intraocular Retinoblastoma Classification. LIC=low-income country. LMIC=lower-middle-income country. UMIC=upper-middle-income country.

secondary education ($\beta=0.67$, $p<0.0001$), birth registration completeness ($\beta=0.75$, $p<0.0001$), maternal mortality rate ($\beta=0.80$, $p<0.0001$), and poverty gap ($\beta=0.60$, $p<0.0001$). Socioeconomic factors showed stronger effect sizes than health-care-specific factors. Multivariable analysis showed that percentage of the population living in rural areas ($\beta=0.42$, $p=0.0005$), Gini index ($\beta=0.31$, $p=0.0001$), and education level of the population, including primary completion rate ($\beta=0.34$, $p=0.0024$), were significant factors affecting overall survival (appendix p 14).

The overall globe salvage rate was positively associated with cataract surgery rate ($\beta=0.43$, $p=0.0003$), eye care worker density ($\beta=0.51$, $p=0.0001$), and education ($\beta=0.54$, $p<0.0001$), but negatively with poverty gap ($\beta=0.46$, $p<0.0001$). Multivariable analysis also showed

the positive association between overall globe salvage rate and secondary school completion rate ($\beta=0.39$, $p=0.022$) and government health-care expenditure ($\beta=0.58$, $p=0.030$; appendix p 14). Looking at advanced intraocular disease globe salvage, a positive association was seen with eye care worker density in the univariate analysis ($\beta=0.56$, $p=0.0027$). Gross national income per capita was the sole significant factor on multivariable analysis ($\beta=0.52$, $p=0.03$; appendix p 14).

Factors with notable effect size in univariable analysis for survival were used to model global survival disparity (appendix p 15). Technical details of training were included in the appendix (pp 11–12). We observed major survival gaps in sub-Saharan Africa and southeast and southwest Asia (figure 3; appendix pp 16–17).

An online dashboard was developed to display the relevant literature findings and modelled survival statistics, which also houses a designated page for comparative system analysis.

Discussion

To our knowledge, our study is the first meta-analysis of the trends and patterns in global retinoblastoma survival and survival disparity over the past 40 years. We found associations between these trends and patterns, and socioeconomic and health-care factors. There have been substantial improvements in global retinoblastoma survival and globe salvage in the past decades, particularly among HICs and UMICs. However, there has been a widening disparity in globe salvage rate over the past decades, with outcomes showing a positive correlation with income level. Improved health-care accessibility and government health-care expenditure were important factors for improving survival, whereas a higher income level and denser health-care worker population were associated with higher globe salvage rates. The improvement in globe salvage rates between 2000–09 and 2010–20 was probably due to gradual but asynchronous adoption of new globe-sparing treatments, such as intra-arterial chemotherapy or plaque radiotherapy. Lower-income regions (LMICs and LICs) continued to have poorer visual outcomes than their higher-income counterparts (HICs or UMICs). We also found major survival gaps in sub-Saharan Africa and southeast and southwest Asia. Delay in reaching a dedicated treatment centre or an absence of such centres, few treatment options available, default on follow-up, and other factors have been suggested to play a part in the poorer outcomes seen in LMICs and LICs.⁷ In addition, cultural and social stigma and belief in alternative treatments had been identified as major reasons for higher enucleation refusal in LMICs than in HICs.⁷⁰ Unfortunately, the present study has not obtained the necessary information to explore the role of sex bias or religion that might have contributed to the poorer outcomes described in these regions. However, we noted that the sex ratios of retinoblastoma cases in parts of sub-Saharan Africa and southeast and southwest Asia were

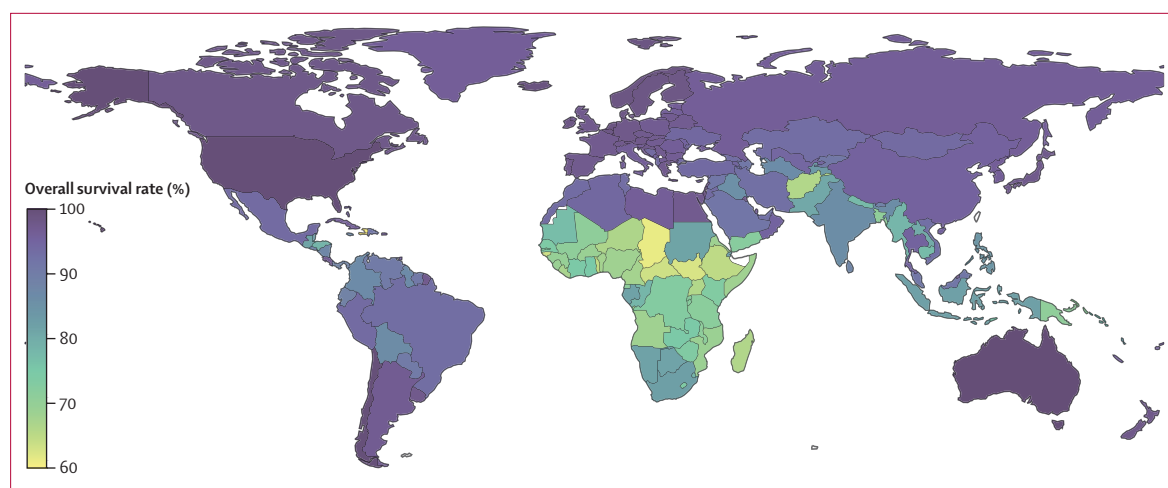


Figure 3: Global retinoblastoma prediction with survival model

Global survival disparity is estimated using a random forest model, using socioeconomic and health-care factors identified in earlier linear regression investigation steps. A darker colour (more purple) shows better estimated survival rates. The predicted survival rate by country is highlighted in the appendix (p 16).

significantly higher than in the rest of the world (1·30 vs 1·14, $p=0\cdot038$), implicating the possible influence of sex bias. Further dedicated investigations are required to address this important issue. Tackling retinoblastoma morbidity globally requires not only financial input but also targeted awareness programmes to improve general knowledge in resource-limited regions in which major disease burden remains.⁷¹

Multivariable analysis showed that gross national income per capita accounted for only a proportion of the heterogeneity in retinoblastoma outcomes. Survival was strongly associated with education level, health-care accessibility (eg, government investment in health care), and disparity in wealth distribution (ie, Gini index). Overall globe salvage rate was also associated with education level and government health-care expenditure, and globe salvage rate for advanced intraocular disease was associated with eye care worker density.

The differential association profiles that we have identified might provide useful information for targeted policy making. For example, technological transfer and financial aid might be necessary for economically deprived regions to boost their globe salvage rates. Improving health-care coverage and expenditure by governments to include all treatment options could also be beneficial. However, clinicians should be aware that the primary goal of treating retinoblastoma is to ensure disease-free survival of the child, whereas globe preservation is the second priority in carefully selected cases. In particular, for advanced intraocular disease (cT3 stage by TNM classification), attempted globe salvage carries a risk of metastasis and lower overall survival than enucleation does, and should be used with extreme caution.⁷²

In localities where government resources are scarce, support from non-governmental organisations, patient care groups, charity funds, and private clinical practices

becomes immensely valuable. These organisations can provide solid platforms for knowledge transfer, external validation, and funding, and can recruit resources and complement governmental efforts to promote treatment access. In Hong Kong, the new Hong Kong Children's Hospital has introduced a dedicated multidisciplinary retinoblastoma clinic jointly managed by ophthalmologists, oncologists, radiologists, and social workers. This model has enabled fast-track subspecialist referral, imaging, and treatment initiation. The Children's Cancer Foundation also sponsors genetic testing for families with financial needs. The globe salvage rate in Hong Kong has subsequently increased from 4·5% in 2008 to 12·5% in 2019 among ICRB group E patients, with a 5-year survival rate of 100% over the years.⁷³ Elsewhere in the world, the Daisy's Eye Cancer Fund devised the Kenyan National Retinoblastoma Strategy, which introduced expertise from Canada and Switzerland, and promoted collaborations with India.⁷⁴

In addition, raising awareness among the general public and health-care workers is important for early diagnosis, which heavily influences treatment success and the prevention of enucleation.⁷ For example, retinoblastoma screening by checking for symmetrical red reflex should be added to routine paediatric health screenings.⁷⁵ Regular health education talks to the general population on retinoblastoma awareness can be coupled with territory-wide outreach and immunisation campaigns to benefit the whole population.⁷⁶ Open access textbooks that allow general ophthalmologists to provide adequate eye care can be produced.⁷⁷ Although low doctor density and poor health-care coverage might make expanded general paediatric screening unfeasible, charity-funded or government-funded subspecialty training programmes to supply ocular oncologists for unserved and underserved countries are effective.⁷⁸ For instance, an outreach project

in Bangladesh yielded a 98% response rate and identified 5% of patients with ocular morbidities,⁷⁹ while retinoblastoma awareness campaigns in Honduras have reduced late presentation from 73% to 35%.⁸⁰ It is important to help parents to identify red-flag symptoms and encourage their use of patient support services. Other successful approaches include expanding the capacities of telemedicine and cloud-based health record systems (eg, mNavigator in Tanzania),⁸¹ developing low-cost screening systems based on artificial intelligence (eg, MDEyeCare and CRADLE in the USA),^{82,83} expanding primary care and health insurance coverage (Taiwan),⁸⁴ and twinning programmes to obtain more than doubled outcomes.⁸⁵ Moreover, prospective collection of uniform, multicentre, international retinoblastoma data and literature are helpful to raise awareness and guide government policy. To devise future research priorities, patients' opinions, especially those with lived experience, should be incorporated. In Canada, the Canadian Retinoblastoma Research Advisory Board Priority Setting Steering Committee determined the top research priorities for retinoblastoma through a partnership between clinicians, researchers, and patients. This partnership provides important support to patients and their families throughout their treatment and rehabilitation processes.⁸⁶ The ongoing efforts to improve retinoblastoma outcomes globally are summarised in the appendix (p 18).

The *Lancet Global Health* Commission for eye health⁸⁷ has shown that eye health is underfunded in many LMICs and LICs; however, the scarcity of cost-effectiveness data, especially for these regions, has made it difficult to elucidate global disparity in eye health outcomes. Retinoblastoma is a highly treatable, well studied, and well reported eye cancer. Our systematic review and meta-analysis showed trends in global retinoblastoma outcomes, and modelled survival disparity with system-level social and health-care infrastructure competence. We used an ecological approach to estimate global disparity and to investigate how country-level social infrastructure could lead to such deviances in a particular period or across the decades.

There are limitations in this study. Although we evaluated a large cohort of more than 20 000 patients, the ecological study approach limited the interpretation of results to the population level. Thus, the observed associations cannot be directly applied to predict the prognosis of individual patients. For the meta-analysis design, we pooled data from multiple studies, each having its own data collection guidelines. This pooling could have introduced heterogeneities in the primary outcome as artifacts of the different approaches of individual studies. The absence of information on both survival and globe salvage in some studies and absence of standardisation in staging criteria between studies might have obscured some of the findings. The TNM staging system has been validated to predict globe salvage, and we propose universal adoption of this

classification system to clarify outcome reporting and improve future research and patient care.^{78,88–90} Patients included in this systematic review and meta-analysis attended health-care facilities that were predominantly tertiary centres and might not precisely represent the country-wide scenario of other locations. Lastly, some participants might have been included in more than one study.

Despite the narrowing of the global survival gap for retinoblastoma over the past decades, disparity for overall and advanced intraocular disease globe salvage rates have widened. Health-care accessibility and government health-care expenditure are important factors influencing survival, and national income level and health-care worker density strongly influence globe salvage rate. Targeted policy making is needed to improve global retinoblastoma treatment outcomes. Active participation by non-government organisations and community activities are helpful to raise awareness.

Contributors

ESW, RWC, and JCY accessed and verified the data, and conceptualised and designed the study. ESW, RWC, and YZ designed the analysis plan, and collected the data for the study. ESW and RWC led the implementation of this study, analysed the data, and wrote the first draft of the manuscript. RWC provided data management. WKC, LJC, CCP, and JCY provided supervision. CCP and JCY obtained funding for this study. YZ, WKC, LJC, CCP, and JCY reviewed and edited the manuscript. JCY was responsible for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data collected for this study are available for sharing. Extracted data from articles included in this Article are available for sharing, from 3 months and until 5 years after article publication. The study protocol is available by request to the corresponding author. An online dashboard was developed to display the relevant literature findings and modelled survival statistics. The dashboard also houses a designated page for comparative system analysis (https://cuhkdovs.shinyapps.io/RB_Data_Studio/). The above data are available for researchers who provide a methodologically sound proposal, for achieving aims in the approved proposal. Proposals should be directed to the corresponding author at yamcheuksing@cuhk.edu.hk.

Acknowledgments

The study was supported in part by the Health and Medical Research Fund Hong Kong (PR-HKCH-8 and 07180306 for JCY) and by a Paediatric Oncology Research Grant from the Children's Cancer Foundation.

References

- 1 Delhiwala KS, Vadakkal IP, Mulay K, Khetan V, Wick MR. Retinoblastoma: an update. *Semin Diagn Pathol* 2016; **33**: 133–40.
- 2 Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am* 2005; **18**: 41–53, viii.
- 3 Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology* 2006; **113**: 2276–80.
- 4 Shields CL, Shields JA. Recent developments in the management of retinoblastoma. *J Pediatr Ophthalmol Strabismus* 1999; **36**: 8–18, quiz 35–36.
- 5 Fabian ID, Onadim Z, Karaa E, et al. The management of retinoblastoma. *Oncogene* 2018; **37**: 1551–60.
- 6 Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: a 2020 review. *Indian J Ophthalmol* 2020; **68**: 2356–65.

- 7 Fabian ID, Abdallah E, Abdullahi SU, et al. Global retinoblastoma presentation and analysis by national income level. *JAMA Oncol* 2020; **6**: 685–95.
- 8 Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. *Br J Ophthalmol* 2010; **94**: 1432–36.
- 9 Abramson DH, Shields CL, Jabbour P, et al. Metastatic deaths in retinoblastoma patients treated with intraarterial chemotherapy (ophthalmic artery chemosurgery) worldwide. *Int J Retina Vitreous* 2017; **3**: 40.
- 10 Beer Prydz E, Wadhwa D. Classifying countries by income. Sept 9, 2019. <https://datatopics.worldbank.org/world-development-indicators/stories/the-classification-of-countries-by-income.html> (accessed Oct 8, 2021).
- 11 Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. *Lancet Oncol* 2014; **15**: 35–47.
- 12 MacCarthy A, Draper GJ, Steliarova-Foucher E, Kingston JE. Retinoblastoma incidence and survival in European children (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006; **42**: 2092–102.
- 13 Luna-Fineman S, Alejos A, Amador G, et al. Improving retinoblastoma outcomes in low income countries: results from the AHOPCA II study in central America. *Pediatr Blood Cancer* 2012; **59**: 985.
- 14 Gündüz AK, Mirzayev I, Temel E, et al. A 20-year audit of retinoblastoma treatment outcomes. *Eye (Lond)* 2020; **34**: 1916–24.
- 15 Goolam S, Kana H, Welsh N, Wainwright L, Poole J, Mayet I. A 20-year retrospective review of retinoblastoma at two tertiary academic hospitals in Johannesburg, South Africa. *Ocul Oncol Pathol* 2018; **4**: 170–75.
- 16 Frenkel S, Weintraub M, Rot I, Shoshani N, Pe'er J. Advances in the treatment of retinoblastoma at Hadassah in the last three decades. *Harefuah* 2018; **157**: 149–53 (in Hebrew).
- 17 Ghassemi F, Chams H, Sabour S, et al. Characteristics of germline and non-germline retinoblastomas. *J Ophthalmic Vis Res* 2014; **9**: 188–94.
- 18 Schindler M, Belle FN, Grotzer MA, von der Weid NX, Kuehni CE. Childhood cancer survival in Switzerland (1976–2013): time-trends and predictors. *Int J Cancer* 2017; **140**: 62–74.
- 19 Stones DK, De Bruin GP, Esterhuizen TM, Stefan DC. Childhood cancer survival rates in two South African units. *S Afr Med J* 2014; **104**: 501–04.
- 20 Navo E, Teplisky D, Alberio R, Fandino AC, Demirdjian G, Chantada GL. Clinical presentation of retinoblastoma in a middle-income country. *J Pediatr Hematol Oncol* 2012; **34**: e97–101.
- 21 Kim H, Lee JW, Kang HJ, et al. Clinical results of chemotherapy-based treatment in retinoblastoma patients: a single center experience. *Cancer Res Treat* 2008; **40**: 164–71.
- 22 Bai S, Ren R, Li B, et al. Delay in the diagnosis of retinoblastoma in China. *Acta Ophthalmol* 2011; **89**: e72–74.
- 23 Rodrigues KE, Latorre MR, de Camargo B. Delayed diagnosis in retinoblastoma. *J Pediatr (Rio J)* 2004; **80**: 511–16 (in Portuguese).
- 24 Reddy VAP, Honavar S, Fairouz PM, Ali MJ, Vemuganti GK. Demographics, treatment, and outcome of retinoblastoma: a large series with protocol-based management. *J Clin Oncol* 2012; **30** (suppl): 9568.
- 25 Kebudi R, Alkaya DU. Epidemiology and survival of childhood cancer in Turkey. *Pediatr Blood Cancer* 2021; **68**: e28754.
- 26 Fernández Fastuca Dres L, Sgroi M, Fandiño AC, Sampor C, Esquivel Y, Chantada G. Evaluación de secuelas visuales y cosméticas del tratamiento conservador con terapia radiante externa en pacientes con retinoblastoma bilateral en el Hospital de Pediatría Garrahan. *Med Infant* 2015; **22**: 88–92.
- 27 Frenkel S, Zloto O, Sagi M, Fraenkel A, Pe'er J. Genotype–phenotype correlation in the presentation of retinoblastoma among 149 patients. *Exp Eye Res* 2016; **146**: 313–17.
- 28 Temming P, Arendt M, Viehmann A, et al. How eye-preserving therapy affects long-term overall survival in heritable retinoblastoma survivors. *J Clin Oncol* 2016; **34**: 3183–88.
- 29 Ljungman G, Jakobson A, Behrendtz M, et al. Incidence and survival analyses in children with solid tumours diagnosed in Sweden between 1983 and 2007. *Acta Paediatr* 2011; **100**: 750–57.
- 30 Saw SM, Tan N, Lee SB, Au Eong KG, Chia KS. Incidence and survival characteristics of retinoblastoma in Singapore from 1968–1995. *J Pediatr Ophthalmol Strabismus* 2000; **37**: 87–93.
- 31 Seregard S, Lundell G, Svedberg H, Kivelä T. Incidence of retinoblastoma from 1958 to 1998 in Northern Europe: advantages of birth cohort analysis. *Ophthalmology* 2004; **111**: 1228–32.
- 32 Tulla M, Berthold F, Graf N, et al. Incidence, trends, and survival of children with embryonal tumors. *Pediatrics* 2015; **136**: e623–32.
- 33 Wongmas P, Jetsrisuparb A, Komvilaisak P, et al. Incidences, trends and long term outcomes of retinoblastoma in three cancer registries, Thailand. *Asian Pac J Cancer Prev* 2015; **16**: 6899–902.
- 34 El-Hayek M, Trad O, Donner M, Hardy D. Pediatric oncology in the United Arab Emirates: the Tawam hospital experience. *Med Pediatr Oncol* 2003; **41**: 486–87.
- 35 Seth R, Singh A, Guru V, Chawla B, Pathy S, Sapra S. Long-term follow-up of retinoblastoma survivors: experience from India. *South Asian J Cancer* 2017; **6**: 176–79.
- 36 Mallipatna AC, Sutherland JE, Gallie BL, Chan H, Héon E. Management and outcome of unilateral retinoblastoma. *J AAPOS* 2009; **13**: 546–50.
- 37 Orman A, Koru-Sengul T, Miao F, Markoe A, Panoff JE. The modern role of radiation therapy in treating advanced-stage retinoblastoma: long-term outcomes and racial differences. *Int J Radiat Oncol Biol Phys* 2014; **90**: 1037–43.
- 38 Committee for the National Registry of Retinoblastoma. The National Registry of Retinoblastoma in Japan (1983–2014). *Jpn J Ophthalmol* 2018; **62**: 409–23.
- 39 Verma N, Murthy DP, Kerek A. Orbital malignancy in Papua New Guinea: a 21 year review. *Aust N Z J Ophthalmol* 1999; **27**: 27–31.
- 40 Bosaleh A, Sampor C, Solernou V, et al. Outcome of children with retinoblastoma and isolated choroidal invasion. *Arch Ophthalmol* 2012; **130**: 724–29.
- 41 Bas Z, Dalvin LA, Tadepalli S, et al. Outcomes of intravenous chemotherapy (chemoreduction) for retinoblastoma based on patient age in 964 eyes of 554 patients. *Asia Pac J Ophthalmol (Phila)* 2021; **10**: 373–80.
- 42 Babatunde TO, Akang EE, Ogun GO, Brown BJ. Pattern of childhood cancer in University College Hospital, Ibadan during 1991–2010 and comparison with the previous three decades. *Paediatr Int Child Health* 2015; **35**: 144–50.
- 43 Kebudi R, Uludağ Alkaya D. Pediatric blood and cancer epidemiology and survival of childhood cancer in Turkey. *Pediatr Blood Cancer* 2020; **68**: e28754.
- 44 Shields CL, Shields JA, Cater J, Othmane I, Singh AD, Micaily B. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001; **108**: 2116–21.
- 45 Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW 3rd. Presenting signs of retinoblastoma. *J Pediatr* 1998; **132**: 505–08.
- 46 Palazzi MA, Stephan C, Brandalise SR, Aguiar SS. Retinoblastoma diagnosis: a proposal based on the experience of Centro Infantil Boldrini, Brazil. *Pediatr Hematol Oncol* 2013; **30**: 379–85.
- 47 Selistre SGA, Maestri MK, Santos-Silva P, et al. Retinoblastoma in a pediatric oncology reference center in Southern Brazil. *BMC Pediatr* 2016; **16**: 48.
- 48 Nummi K, Kivelä TT. Retinoblastoma in Finland, 1964–2014: incidence and survival. *Br J Ophthalmol* 2021; **105**: 63–69.
- 49 Traboulsi EI, Jurdi-Nuwayhid F, Frangieh GT, Der Kaloustian VM. Retinoblastoma in Lebanon. *Ophthalmic Paediatr Genet* 1986; **7**: 29–34.
- 50 Chuluunbat T, Jamiyanjav B, Munkhuu B, et al. Retinoblastoma in Mongolia: clinical characteristics and survival from 1987 to 2014. *Taiwan J Ophthalmol* 2016; **6**: 79–84.
- 51 Azar D, Donaldson C, Kalapesi F, Cumming R. Retinoblastoma in New South Wales 1975 to 2001. *J Pediatr Hematol Oncol* 2006; **28**: 642–46.
- 52 Pedram M, Arash A, Salari F, et al. Retinoblastoma in southwest Iran. *IJBC* 2015; **7**: 143–48.
- 53 Chang CY, Chiou TJ, Hwang B, Bai LY, Hsu WM, Hsieh YL. Retinoblastoma in Taiwan: survival rate and prognostic factors. *Jpn J Ophthalmol* 2006; **50**: 242–49.

- 54 Kazadi Lukusa A, Aloni MN, Kadima-Tshimanga B, et al. Retinoblastoma in the Democratic Republic of Congo: 20-year review from a tertiary hospital in Kinshasa. *J Cancer Epidemiol* 2012; **2012**: 920468.
- 55 Günalp I, Gündüz K, Arslan Y. Retinoblastoma in Turkey: diagnosis and clinical characteristics. *Ophthalmic Genet* 1996; **17**: 21–27.
- 56 Ozkan A, Pazarli H, Celkan T, et al. Retinoblastoma in Turkey: survival and clinical characteristics 1981–2004. *Pediatr Int* 2006; **48**: 369–73.
- 57 Mouratova T. Retinoblastoma in Uzbekistan. *Bull Soc Belge Ophthalmol* 2003; **289**: 63–69.
- 58 Sukumaran DO. Retinoblastoma—a 20 year review from the University Hospital Kuala Lumpur. *Med J Malaysia* 1991; **46**: 129–35.
- 59 Sovinz P, Urban C, Lackner H, Benesch M, Langmann G. Retinoblastoma: a proposal for a multimodal treatment concept for intraocular retinoblastoma in Austria. *Wien Klin Wochenschr* 2006; **118**: 22–30.
- 60 Kabre RS, Kamble KM. Retinoblastoma: a retrospective analysis of 141 patients from 1983 to 2013 at a tertiary care hospital in Nagpur, India. *South Asian J Cancer* 2019; **8**: 195–97.
- 61 da Rocha-Bastos R, Araújo J, Silva R, et al. Retinoblastoma: experience of a referral center in the North region of Portugal. *Clin Ophthalmol* 2014; **8**: 993–97.
- 62 Arif M, Islam Z. Retinoblastoma: postenucleation orbital recurrence. *Can J Ophthalmol* 2010; **45**: 606–09.
- 63 Saakyan S, Myakoshina E, Ismailova D. Retinopathy in young retinoblastoma patients receiving a chemotherapy treatment: clinical trials and morphometric analysis. *Ophthalmic Genet* 2019; **40**: 521–33.
- 64 Yang IH, Kuo HK, Chen YJ, Lee JJ, Lin SA. Review of 20 years' clinical experience with retinoblastomas in southern Taiwan. *Chang Gung Med J* 2008; **31**: 484–91.
- 65 Suzuki S, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. *Ophthalmology* 2011; **118**: 2081–87.
- 66 Wallach M, Balmer A, Munier F, et al. Shorter time to diagnosis and improved stage at presentation in Swiss patients with retinoblastoma treated from 1963 to 2004. *Pediatrics* 2006; **118**: e1493–98.
- 67 Ueda T, Koga Y, Yoshikawa H, et al. Survival and ocular preservation in a long-term cohort of Japanese patients with retinoblastoma. *BMC Pediatr* 2020; **20**: 37.
- 68 Joko-Fru WY, Parkin DM, Borok M, et al. Survival from childhood cancers in Eastern Africa: a population-based registry study. *Int J Cancer* 2018; **143**: 2409–15.
- 69 Asencio-López L, Torres-Ojeda AA, Isaac-Otero G, Leal-Leal CA. Treating retinoblastoma in the first year of life in a national tertiary paediatric hospital in Mexico. *Acta Paediatr* 2015; **104**: e384–87.
- 70 Olteanu C, Dimaras H. Enucleation refusal for retinoblastoma: a global study. *Ophthalmic Genet* 2016; **37**: 137–43.
- 71 Fabian ID, Abdallah E, Abdullahi SU, et al. Global retinoblastoma presentation and analysis by national income level. *JAMA Oncol* 2020; **6**: 685–95.
- 72 Abramson DH, Fabius AW, Issa R, et al. Advanced unilateral retinoblastoma: the impact of ophthalmic artery chemosurgery on enucleation rate and patient survival at MSKCC. *PLoS One* 2015; **10**: e0145436.
- 73 Wong ES, Chan AYY, Lam CPS, Lau WWY, Yam JCS, Yu CBO. Retinoblastoma in Hong Kong from 2008 to 2019: looking back and moving forward. *Hong Kong J Ophthalmol* 2020; **24**: 6–10.
- 74 Hill JA, Kimani K, White A, et al. Achieving optimal cancer outcomes in East Africa through multidisciplinary partnership: a case study of the Kenyan National Retinoblastoma Strategy group. *Global Health* 2016; **12**: 23.
- 75 Mndeme FG, Mgaya E, Allen L, Bowman R. Red reflex examination in reproductive and child health clinics for early detection of paediatric cataract/ocular media disorders: evidence from Kilimanjaro, Tanzania. *J AAPOS* 2018; **22**: e4.
- 76 Wilimas JA, Wilson MW, Haik BG, et al. Development of retinoblastoma programs in central America. *Pediatr Blood Cancer* 2009; **53**: 42–46.
- 77 Chaugule SS, Honavar SG, Finger PT. Surgical ophthalmic oncology: a collaborative open access reference. Cham: Springer International Publishing, 2019.
- 78 Tomar AS, Finger PT, Gallie B, et al. A multicenter, international collaborative study for American Joint Committee on Cancer staging of retinoblastoma, part I: metastasis-associated mortality. *Ophthalmology* 2020; **127**: 1719–32.
- 79 Hussain AHME, Roy T, Ferdausi N, Sen U. Prevalence of childhood ocular morbidity in a peri-urban setting in Bangladesh: a community-based study. *Public Health* 2019; **170**: 103–12.
- 80 Leander C, Fu LC, Peña A, et al. Impact of an education program on late diagnosis of retinoblastoma in Honduras. *Pediatr Blood Cancer* 2007; **49**: 817–19.
- 81 Vasudevan L, Schroeder K, Raveendran Y, et al. Using digital health to facilitate compliance with standardized pediatric cancer treatment guidelines in Tanzania: protocol for an early-stage effectiveness-implementation hybrid study. *BMC Cancer* 2020; **20**: 254.
- 82 Khedekar A, Devarajan B, Ramasamy K, Muthukkaruppan V, Kim U. Smartphone-based application improves the detection of retinoblastoma. *Eye (Lond)* 2019; **33**: 896–901.
- 83 Munson MC, Plewman DL, Baumer KM, et al. Autonomous early detection of eye disease in childhood photographs. *Sci Adv* 2019; **5**: eaax6363.
- 84 Su WW, Kao LY. Retinoblastoma in Taiwan: the effect of a government-sponsored national health insurance program on the treatment and survival of patients with retinoblastoma. *J Pediatr Ophthalmol Strabismus* 2006; **43**: 358–62.
- 85 Rodriguez-Galindo C, Wilson MW, Chantada G, et al. Retinoblastoma: one world, one vision. *Pediatrics* 2008; **122**: e763–70.
- 86 Flegg K, Gelkopf MJ, Johnson SA, Dimaras H. The top 10 retinoblastoma research priorities in Canada as determined by patients, clinicians and researchers: a patient-oriented priority-setting partnership. *CMAJ Open* 2020; **8**: E420–28.
- 87 Burton MJ, Ramke J, Marques AP, et al. The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. *Lancet Glob Health* 2021; **9**: e489–551.
- 88 Tomar AS, Finger PT, Gallie B, et al. A multicenter, international collaborative study for American Joint Committee on Cancer staging of retinoblastoma, part II: treatment success and globe salvage. *Ophthalmology* 2020; **127**: 1733–46.
- 89 Tomar AS, Finger PT, Gallie B, et al. Global retinoblastoma treatment outcomes: association with national income level. *Ophthalmology* 2021; **128**: 740–53.
- 90 Tomar AS, Finger PT, Gallie B, et al. Retinoblastoma seeds: impact on American Joint Committee on Cancer clinical staging. *Br J Ophthalmol* 2021; published online Aug 2. <https://doi.org/10.1136/bjophthalmol-2021-318892>.