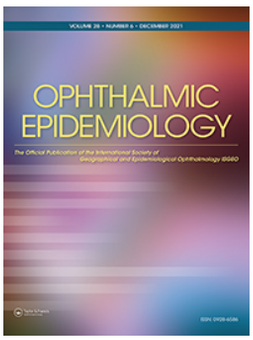

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The Incidence of Retinoblastoma in South Africa: Findings from the South African National Cancer Registry (2004–2018)

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ABSTRACT

Purpose: To determine the frequency and incidence rate of retinoblastoma in children in South Africa from 2004 to 2018.

Methods: Incident cases of histologically diagnosed retinoblastoma were identified from the South African National Cancer Registry. Crude incidence rates were calculated using national population data on children <15 years and live births. Incidence rates were stratified and compared by age, sex and population group. Direct age-standardised incidence rates and comparative incidence ratios were calculated.

Results: The overall age-standardised incidence rate for children <15 years was 3.3 per million or 1 per 21 641 live births. Age-specific rates for children aged 0–4, 5–9 and 10–14 years were 7.7, 0.8 and 0.2 per million, respectively. There was no difference in incidence rates by sex. White children had a significantly higher incidence rate compared to other population groups, but this finding may be due to systemic biases introduced by access to healthcare in South Africa or study methodology.

Conclusion: This is the largest study to provide population-based, histologically confirmed national estimates of retinoblastoma incidence from an African nation to date and affirms the need for high-quality cancer registries across the African continent.

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Retinoblastoma; incidence; South Africa; epidemiology; National Cancer Registry

Introduction

Retinoblastoma is the most frequent primary intra-ocular malignancy of childhood and one of the most common paediatric cancers, accounting for 11% of all malignancies diagnosed in the first year of life.[1] In high-income countries (HIC), 95% of cases are diagnosed before the age of 5 years with survival rates >95%.[1,2] However, an estimated 89% of all affected children globally reside in low- and middle-income countries (LMIC), where gaps in access to specialised healthcare are associated with late clinical presentation and substantially lower patient survival.[2]

The estimated incidence of retinoblastoma is similar across most epidemiological studies with no validated evidence of geographic or racial variation.[2] Reliable estimates, however, require a representative national registry system or a large claim database. Less than 10% of people living in LMIC are covered by high-quality, population-based cancer registries[3] and, consequently, most figures are derived from HIC with an estimated incidence of 10–12 per million for children aged 0–4 years, or 1 case per 15 000–20 000 live births.[2,4–6] There is a paucity of data from LMIC, and specifically from African nations, with significant variability in reported rates from various sub-Saharan cancer registries.[7] This is in stark contrast to the largely similar rates observed in HIC.

South Africa is a middle-income country (MIC) with a diverse, multi-racial population of approximately 60 million. It is serviced by a dual public-private healthcare system and is characterised by vast inequities in access to healthcare, largely divided along racial lines.[8] There have been no previous histologically confirmed, population-based estimates of retinoblastoma incidence in South Africa. Using a pathology-based national cancer registry database, we investigated the incidence of retinoblastoma in South Africa over a 15-year period (2004–2018).

Methods

Data sources

Anonymised data on incident retinoblastoma cases were obtained from the South African National Cancer Registry (NCR), a division of the National Health Laboratory

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Service (NHLS). The history, objectives and methodology of the NCR have been reported previously.[9–11] Briefly, the NCR was established in 1986 as a pathology-based cancer registry that collects data on all cytologically and histologically diagnosed invasive malignancies from public and private healthcare laboratories in South Africa. Since 2011, legislation has formally established the NCR as South Africa's main cancer surveillance agency, with obligatory reporting of all confirmed cancer cases.

Demographic and tumour information are extracted from all pathology reports submitted to the NCR. Demographic details include age, sex and population group (Black, White, Coloured [mixed race] and Asian/Indian) as used for the South African national census. A hot-deck imputation method is used to allocate missing population group data (based on known surname–population group pairings) but does not always succeed in allocating this information. Cancer topographies and morphologies are coded according to the International Classification of Diseases for Oncology Version 3 (ICD-O3), but exclude information on tumour clinical grade or stage. The entire dataset from inception is reviewed for duplicates to ensure only incident cancer cases are retained.

Population data were obtained from published Statistics South Africa (SSA) reports (available at www.statssa.gov.za). This included mid-year population estimates based on national census and community survey data (stratified by 5-year age groups, sex and population group) and annual live births based on legislated reporting of vital statistics (stratified by sex).

Statistical analysis

Incident cases of retinoblastoma (ICD-O3 morphology codes 9510–9514) occurring in children <15 years of age from 2004 to 2018 were identified and extracted from the NCR database. Since the occurrence of retinoblastoma in individuals ≥15 years is exceptionally rare, all cases occurring in individuals ≥15 years were excluded from this analysis and reported to the NCR for independent verification.[12] Similarly, all cases with missing information on age of diagnosis were assumed to have occurred in individuals <15 years of age.

The study period was divided into five 3-year time periods: 2004–2006, 2007–2009, 2010–2012, 2013–2015 and 2016–2018. Crude age-specific incidence rates with 95% confidence intervals (CI) for each period were calculated using mid-year population estimates as denominators for the 0–4, 5–9 and 10–14 year age groups. These age groups were labelled according to the convention used by SSA and the International Agency for Research on Cancer (IARC) and include children aged 0–<5, 5–<10 and 10–<15 years, respectively. Incidence rates were further stratified and compared by sex and population group. Direct standardisation (Segi World Standard Population) was employed to calculate age-standardised incidence rates (ASIR) for children <15 years for each time period and the overall study period. Comparative incidence figures (CIF) with 95% CI were calculated.[13] The CIF is a ratio of two age-standardised rates, analogous to an incidence rate ratio. Rates were considered significantly different if the 95% CI of the CIF did not include a ratio of 1.00.

When calculating age-, sex- and population group-specific incidence rates, the pro rata method of allocating cancers was employed when this information was missing. This method, recommended by the IARCand standard NCR methodology, allocates cancers proportionately according to the observed frequency of the missing demographic parameters in the remaining dataset.[11,14]

Incidence per number of live births was estimated using standard annual analysis (total cases in each time period divided by total live births in that period).

Incidence rates were expressed as cases per million with 95% CI. All analyses were conducted using Microsoft Excel (Microsoft Corp. 2019. Redmond, WA, USA) and Stata (Version 16.0. StataCorp LLC. 2019. College Station, TX, USA).

Ethical considerations

The research adhered to the tenets of the Declaration of Helsinki and ethical approval was granted by the Health Sciences Research Ethics Committee, University of the Free State (UFS-HSD2020/0611/2605-0001). No personally identifiable data was utilised for this study.

Results

In total, 709 cases of retinoblastoma were identified from 2004 to 2018 in the South African NCR. Five cases (0.7%) were excluded based on an age of diagnosis ≥15 years. Data on age of diagnosis, sex and population group were missing in 20 (2.8%), 5 (0.7%) and 39 (5.5%) cases, respectively. These cases were included in the main analysis and handled according to the methods discussed above.

Based on cases with complete demographic information, the proportion of diagnoses occurring in the 0–4, 5–9 and 10–14 year age groups were 88.7%, 9.2% and 2.0%, respectively, with a mean age of diagnosis of

2.5 years. Males comprised 52.6% of all cases. The population distribution was 84.2% Black, 7.2% White, 7.1% Coloured and 1.5% Asian/Indian.

The overall age-specific incidence rate of retinoblastoma for the study period was 7.7 (95% CI, 7.1–8.3), 0.8 (95% CI, 0.6–1.0) and 0.2 (95% CI, 0.1–0.3) per million for the 0–4, 5–9 and 10–14 age groups, respectively; equating to an ASIR of 3.3 (95% CI, 3.1–3.5) per million for children <15 years.

The sex-specific ASIR for retinoblastoma in children <15 years for the study period was 3.5 (95% CI, 3.2–3.7) and 3.1 (95% CI, 2.9–3.5) for males and females, respectively. This equated to a CIF of 1.10 (95% CI, 0.95–1.24) for the study period. There was no significant difference in incidence rates by sex for any age group or time period. Detailed age- and sex-specific frequencies and incidence rates for each 3-year time period are provided in Table 1.

The population group-specific ASIR for retinoblastoma in children <15 years for the study period was 3.2 (95% CI, 3.0–3.5), 5.1 (95% CI, 4.0–6.2), 2.9 (95% CI, 2.3–3.7) and 2.8 (95% CI, 1.5–4.4) per million for Black, White, Coloured and Asian/Indian children, respectively. The rate observed in White children was significantly higher than in Black children (CIF 1.57, 95% CI 1.29–1.86), Coloured children (CIF 1.74, 95% CI 1.36–2.13) and Asian/Indian children (CIF 1.81, 95% CI 1.15–2.47). There were no significant differences in rates between any other population groups. Detailed age- and population group-specific frequencies and incidence rates for the study period are provided in Table 2.

The total incidence for 2004–2018 was 46.2 (95% CI, 42.9–49.8) per million live births, corresponding to 1 case per 21 641 (95% CI, 20 099–23 333) live births. Detailed sex-specific incidence per live births in each 3-year period are provided in Table 3.

Discussion

This study provides the first nationally representative, histology-based estimates of retinoblastoma incidence in South Africa, including detailed estimates of age-, sex- and population group-specific rates.

Findings from this study differ from international figures in a number of ways. The mean age of diagnosis in the South African NCR was 2.5 years, with 88.7% of cases diagnosed before the age of 5 years. This is considerably higher than that observed in HIC where the

Table 1. Number of retinoblastoma cases recorded in the South African National Cancer Registry and the incidence rate of retinoblastoma in South Africa (2004–2018) by age, sex and time period.

	Total		Male		Female	
Age (years)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)
2004–2006						
0–4	115	7.9 (6.6–9.3)	63	8.7 (6.8–10.9)	51	7.1 (5.3–8.9)
5–9	16	1.1 (0.6–1.7)	7	1.1 (0.5–1.9)	8	1.2 (0.5–2.0)
10–14	5	0.3 (0.1–0.7)	2	0.1 (0.0–0.3)	3	0.4 (0.1–0.9)
ASIR 0–14	144	3.5 (3.0–4.0)	77	3.8 (3.2–4.3)	65	3.2 (2.6–3.9)
2007–2009						
0–4	108	7.1 (5.9–8.5)	50	6.8 (5.1–8.7)	56	7.5 (5.7–9.5)
5–9	8	0.5 (0.2–0.9)	3	0.4 (0.1–0.9)	5	0.7 (0.2–1.3)
10–14	3	0.2 (0.0–0.5)	2	0.3 (0.0–0.7)	1	0.1 (0.0–0.5)
ASIR 0–14	121	3.0 (2.5–3.5)	57	2.8 (2.2–3.5)	62	3.1 (2.5–3.9)
2010–2012						
0–4	141	9.2 (7.8–10.8)	71	9.2 (7.2–11.4)	69	9.3 (7.2–11.4)
5–9	11	0.7 (0.3–1.2)	7	0.9 (0.4–1.6)	4	0.5 (0.1–1.1)
10–14	2	0.1 (0.0–0.4)	1	0.1 (0.0–0.5)	1	0.1 (0.0–0.5)
ASIR 0–14	157	3.8 (3.3–4.4)	80	3.9 (3.2–4.7)	76	3.8 (3.1–4.5)
2013–2015						
0–4	123	7.5 (6.2–8.8)	68	8.3 (6.4–10.2)	55	6.6 (5.0–8.5)
5–9	19	1.2 (0.7–1.8)	7	0.9 (0.4–1.6)	12	1.5 (0.8–2.4)
10–14	4	0.3 (0.1–0.6)	2	0.3 (0.0–0.7)	2	0.3 (0.0–0.7)
ASIR 0–14	150	3.4 (2.9–3.9)	80	3.6 (2.9–4.3)	70	3.1 (2.5–3.8)
2016–2018						
0–4	120	7.0 (5.8–8.2)	69	8.0 (6.2–9.9)	51	5.9 (4.4–7.6)
5–9	9	0.5 (0.2–0.9)	3	0.4 (0.1–0.8)	6	0.7 (0.3–1.3)
10–14	0	-	0	-	0	-
ASIR 0–14	132	2.9 (2.4–3.3)	74	3.2 (2.6–3.9)	58	2.5 (2.0–3.1)
2004–2018						
0–4	607	7.7 (7.1–8.3)	321	8.2 (7.4–9.1)	282	7.2 (6.4–8.1)
5–9	63	0.8 (0.6–1.0)	27	0.7 (0.5–1.0)	35	0.9 (0.6–1.2)
10–14	14	0.2 (0.1–0.3)	7	0.2 (0.1–0.3)	7	0.2 (0.1–0.3)
ASIR 0–14	704	3.3 (3.1–3.5)	368	3.5 (3.2–3.7)	331	3.1 (2.9–3.5)

N, number of cases. IR, incidence rate. Rates expressed are age-specific crude incidence rates for the 0–4, 5–9 and 10–14 year age groups and age-standardised incidence rates (ASIR) for the overall 0–14 year age group. All incidence rates are reported as cases per million ± 95% confidence intervals (CI). Cases with unknown age of diagnosis are included in the calculation of the overall 0–14 year ASIR.

Table 2. Number of retinoblastoma cases recorded in the South African National Cancer Registry and the incidence rate of retinoblastoma in South Africa (2004–2018) by age and population group.

	Black		White		Coloured		Asian/Indian	
Age (years)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)
0–4	484	7.6 (6.9–8.2)	41	12.1 (8.9–15.8)	40	6.7 (4.8–8.8)	9	6.6 (2.9–11.0)
5–9	50	0.8 (0.6–1.1)	3	0.8 (0.1–1.7)	3	0.5 (0.1–1.1)	1	0.8 (0.0–2.6)
10–14	9	0.1 (0.1–0.2)	2	0.5 (0.1–1.2)	3	0.5 (0.1–1.1)	0	-
ASIR 0–14	560	3.2 (3.0–3.5)	48	5.1 (4.0–6.2)	47	2.9 (2.3–3.7)	10	2.8 (1.5–4.4)

N, number of cases. IR, incidence rate. Rates expressed are age-specific crude incidence rates for the 0–4, 5–9 and 10–14 year age groups and age-standardised incidence rates (ASIR) for the overall 0–14 year age group. All incidence rates are reported as cases per million ± 95% confidence intervals (CI). Cases with unknown age of diagnosis are included in the calculation of the overall 0–14 year ASIR.

Table 3. Incidence of retinoblastoma per live births in South Africa (2004–2018) by sex and time period.

Time period	Total	Male	Female
	Incidence (95% CI)	Incidence (95% CI)	Incidence (95% CI)
2004–2006	1 per 22 021 (18 705–26 112)	1 per 20 395 (16 356–25 825)	1 per 23 957 (18 929–31 199)
2007–2009	1 per 26 539 (22 210–31 983)	1 per 27 866 (21 698–37 027)	1 per 25 332 (19 807–32 979)
2010–2012	1 per 19 678 (16 830–23 159)	1 per 19 341 (15 552–24 375)	1 per 20 035 (16 109–25 591)
2013–2015	1 per 20 036 (17 074–23 672)	1 per 18 935 (15 214–23 879)	1 per 21 294 (16 854–27 316)
2016–2018	1 per 20 894 (17 619–24972)	1 per 18 804 (14 978–23 947)	1 per 23 561 (18 226–31 028)
2004–2018	**1 per 21 641 (20 099–23 333)**	**1 per 20 701 (18 698–22 983)**	**1 per 22 689 (20 404–25 369)**

Incidence expressed as cases per million live births ± 95% confidence intervals (CI) using standard annual analysis.

mean age of diagnosis may be as low as 1.2 years[7] and >95% of cases are diagnosed before the age of 5 years.[2] A higher mean age of diagnosis is consistent across most African cancer registries, with figures ranging from 1.8 to 3.6 years.[7] This finding may be explained by a higher relative frequency of unilateral (sporadic) retinoblastoma cases, which occur at an older age than bilateral (hereditary) cases, and a relatively advanced stage of clinical presentation in Africa.[2,7] However, results from two South African studies[15,16] suggest that the proportion of bilateral cases in the country (31–35%) is similar to that observed in the USA and UK,[6,17] and delayed or advanced presentation is most likely the major contributory factor in this regard – a trend mirrored in most LMIC.[18] The fact that findings from this study are based on histologically confirmed retinoblastoma cases, which by necessity can only occur after clinical presentation, might also play a role. Additionally, as only cases requiring enucleation undergo histopathological testing, there is almost certainly a bias towards advanced disease and older age in histopathological registries.

The overall ASIR for children <15 years in South Africa (3.3 per million) is lower than that observed in HIC where estimates range from 4.6 to 5.2.[7] Similarly, the incidence rate by live births (1 per 21 641) is lower than reported international figures of 1 per 15 000–20 000 live births.[4,5]

Our results are largely consistent with previous estimates of retinoblastoma incidence in South Africa.[7,19] These include ASIRs of 3.3 per million (1987–2007) and 3.2 per million (2008–2012) for children <15 years (both based on data from a central registry of hospital-based registers). One older study reported an incidence of one case per 10 000 live births (1955–1976) but was only based on data from a single large centre.[20]

The reported incidence of retinoblastoma in Africa varies widely between registries, with ASIRs for children <15 years as low as 2.6 per million in Guinea and as high as 27.2 per million in Malawi.[7] Most of these estimates, however, are based on a small total number of cases, with the highest frequency of retinoblastoma (141 cases between 2006 and 2014 in Mali) being a fifth the size of the current study. The majority of these African cancer registries also serve only specific cities, regions or districts and are not nationally representative. Since most are based in large referral centres or capital cities, defining a specific population-at-risk is difficult and may lead to an overestimation of incidence. Reported rates from African cancer registries that do cover entire populations (Mauritius, Botswana, Reunion and The Gambia) range from 3.4 to 6.0 per million and more closely mirror international figures and the results of this study.[7] Alternatively, these differences may be due to geographical variation in certain environmental risk factors (such as viral infections) which are hypothesised to contribute to retinoblastoma pathogenesis.[21]

The lower rates observed in our study likely represent the limitation of our data source, rather than being a true reflection of retinoblastoma incidence in South Africa. Results from pathology-based registries can only be considered to represent the bare minimum confirmed disease burden in a population, since cases that are not histologically or cytologically confirmed are not

included. This therefore excludes cases that: never present to healthcare services; are diagnosed clinically or pathological diagnosis is not indicated; are lost to follow-up or die before pathology is submitted; or where pathology reports are not submitted to the cancer registry for various reasons.

With specific reference to retinoblastoma, this may result in bias towards advanced disease as only enucleated eyes would be captured by a histopathology registry, while cases undergoing globe-sparing therapy would be excluded. In HIC, where early presentation is the norm, this would certainly result in a gross underestimation of true retinoblastoma incidence. Current South African retinoblastoma management protocols advocate local therapy for International Intraocular Retinoblastoma Classification (IIRC) groups A–D, and enucleation for IIRC group E and International Retinoblastoma Staging System (IRSS) stage I and above. Full details of retinoblastoma classification systems and South African treatment protocols can be found elsewhere.[22,23] Previous South African studies have shown that <20% of cases are amenable to local therapy at presentation,[15,16] suggesting that histopathology-derived estimates may be substantially less biased in our setting, and indeed in many LMIC.

Consistent with findings from previous studies, we did not observe any significant difference in retinoblastoma incidence rates by sex.[4,6] A higher rate has been observed in males in the US Surveillance, Epidemiology, and End Results (SEER) Program, however, and it has been suggested that males may be at greater risk for retinoblastoma than females, despite no readily apparent explanation for this finding.[17,24] Although males were more affected than females in our study (CIF 1.10), this was not statistically significant.

Worldwide, the highest rate of retinoblastoma occurs in the 0–4 year age group with reported international figures of 10–12 cases per million.[4,6] Rates in the 5–9 and 10–14 year age groups are far lower (approximately 0.5 and <0.1 cases per million, respectively).[24] Similar to our main finding, we observed a lower rate (7.7 per million) in the 0–4 year age group compared with estimates from HIC, but relatively higher rates were observed in the 5–9 year age group (0.8 per million) and 10–14 year age group (0.2 per million). A similar distribution has been observed in India, another MIC, with reported figures of 9.6, 2.0 and 0.1 per million for the three age groups, respectively.[24] We speculate that this again reflects a later age of clinical presentation in LMIC, where significant barriers to access to healthcare exist, rather than true differences in at-risk age groups.[25]

In our study, White children were found to have a significantly higher rate of retinoblastoma than Black (CIF 1.57), Coloured (CIF 1.74) and Asian/Indian (CIF 1.81) children. This finding should be interpreted with caution, however, as there are various possible underlying explanations. Firstly, the hot deck imputation and pro rata allocation methods used to allocate missing population group information in the South African NCR may introduce significant bias if this data is not correctly allocated or is not missing at random.[26] Secondly, there are well-documented inequities in access to healthcare in South Africa, largely divided along racial lines.[8] These systemic differences in barriers and access to healthcare may mean that White children are more likely to receive specialist and/or private sector diagnosis and management, and hence be more likely to be captured on a national cancer registry, than other population groups. Indeed, the rate observed in White children in South Africa (12.1 per million for children 0–4 years) closely mirrors that reported in children from various HIC.[4] Finally, although a true difference is a possibility, results from both South Africa[19] and the USA SEER Program[17] suggest that White children have a slightly lower retinoblastoma incidence rate than other population groups.

The strengths of this study include the fact that the NCR data upon which it is based are both histologically confirmed and nationally representative, making it the most reliable source of information for estimating cancer incidence in South Africa. In addition, the size and temporal scope of the study allow for reliable estimates, population stratification and make it the largest study of its kind from an African nation.

There are, however, numerous limitations to the study, many of which have already been discussed. These include potential biases introduced by missing data; systemic differences in access to and quality of healthcare; and an under-estimation of the true cancer burden due to a variety of possible factors. Another major limitation is the lack of clinical information attached to each confirmed retinoblastoma case: data on laterality and heritability, tumour grading and staging, clinical management, and long-term follow-up are all not available. Although allowing for an estimation of overall incidence, this limits further analysis to basic demographic variables only. Specialised registries, such as the South African Paediatric Tumour Registry (SAPTR),[9,27] are invaluable to research of these clinical factors. Estimates of retinoblastoma incidence from the SAPTR do not show marked population group differences,[19] but these may be biased in the opposite direction to estimates from this study, as the SAPTR has

extensive public sector coverage. Lastly, the South African NCR has experienced numerous challenges since its inception in 1986, including issues related to administration, funding, leadership, policy and data collection, which limit the reliability of early data.[9] However, the effect of these challenges have been shown to have minimal impact on estimates of cancer incidence during our study period.[10]

Future research will need to confirm the results and trends of this study in subsequent years, and especially from 2011, when mandatory cancer reporting to the NCR was legislated. The use of specialised cancer registries to investigate the effect of population group on various retinoblastoma clinical parameters in South Africa should also be considered. Linkage studies combining the data from both the NCR and the SAPTR would be invaluable to ensuring more complete coverage of national retinoblastoma cases, including those cases diagnosed clinically, and hence better estimates of national incidence rates. This approach is particularly relevant in settings like South Africa where retinoblastoma screening and management continue to improve, and where histopathology registries will consequently provide greater underestimations of retinoblastoma incidence in future.

In conclusion, the overall incidence of retinoblastoma in the South African NCR is lower than reported figures from HIC and likely represents an underestimation of true incidence. The age distribution mirrors results from MIC and is thought to reflect delayed clinical presentation due to barriers in access to healthcare, reinforcing the critical need for early screening programs in order to improve patient care in these settings. Similarly, observed differences in population group-specific rates may be due to bias introduced by racial inequity in access to healthcare or study methodology. This study is the largest of its kind from an African nation to date and affirms the need for high quality, population-based cancer registries across the African continent.

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Data availability

National Cancer Registry data supporting the findings of this study are available on request from Dr Elvira Singh (elviras@nicd.ac.za). Population data supporting the findings of this study were derived from published Statistics South Africa reports and are available in the public domain (www.statssa.gov.za).

Publication statement

This submission has not been published anywhere previously and it is not simultaneously being considered for any other publication.

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