Racial/ethnic disparities in all-cause and cause-specific death among children with malignant central nervous system tumours: a registry-based cohort retrospective analysis

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Summary

Background It is generally recognized that there is unequal mortality in childhood central nervous system (CNS) malignancy in the United States (US), but little is known about the trends and contributors of racial/ethnic disparities in death. We assessed the trends of racial/ethnic disparities in all-cause and cause-specific death, and the contributions of tumour, treatment and socioeconomic factors to this disparity.

Methods This registry-based cohort study included children (aged ≤19 years) diagnosed with malignant CNS tumours, using data from the US population-based cancer registry in the Surveillance, Epidemiology, and End Results (SEER) Program. The clinical outcomes were all-cause and cause-specific death for each racial/ethnic group (White, Black, Hispanic, non-Hispanic Asian/Pacific Islander [API], and non-Hispanic American Indian/Alaska Native [AI/AN] children). We quantified absolute disparities using absolute rate difference in 5-year cumulative incidence of death. Cox proportion risk models were used to estimate the relative racial/ethnic disparities, and the contribution of factors to disparities in death.

Findings In this study, data from 14,510 children with malignant CNS tumours (mean [SD] age, 8.5 [5.7]; 7988 [55.1%] male) were analysed. Overall, the cumulative incidence of death from CNS tumours across four racial/ethnic groups decreased from 2001 to 2020. Black patients had the highest risk of death from all causes and CNS tumours between 2001 and 2020, with adjusted hazard ratios (HR) of 1.52 (1.38–1.68) and 1.47 (1.31–1.64), respectively. The absolute disparity in all-cause death between Hispanic and White patients increased slightly (from 8.2 percentage points [ppt] to 9.4 ppt), and the relative disparity in death from CNS tumours increased from 1.33 (1.15–1.55) in 2001–2005 to 1.78 (1.44–2.20) in 2016–2020. The absolute disparities in death from CNS tumours between Black and White patients (from 11.8 ppt to 4.3 ppt) and between API and White patients (from 10.1 ppt to 5.1 ppt) decreased from 2001–2005 to 2011–2015.

Interpretation Race/ethnicity disparities in death from CNS tumours among childhood malignant CNS tumours had reduced from 2001 to 2020, and quantifying the contribution of factors to this disparity in death could provide a basis for decreasing mortality among racial/ethnic minority patients.

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Keywords: Childhood central nervous-system tumours; Racial/ethnic disparities; Cause-specific death; Mediation analysis

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Research in context

Evidence before this study

Racial/ethnic disparities in death among childhood central nervous system (CNS) tumour have been reported, however, relatively few studies have assessed long-term trends and potential causes of disparities in death among childhood CNS tumour. We searched PubMed from database inception to October 1, 2023, using the search terms "childhood central nervous system neoplasm OR paediatric central nervous system neoplasm", "racial disparity OR racial inequity", and "mortality OR death". Studies were restricted to those in English or with English translations available. Case reports were excluded from the search. Previously published relevant studies have revealed racial/ethnic inequalities in neuro-oncology, and in the resulting inequalities in mortality, but scarce data exists assessing the trends and potential causes of all-cause and cause-specific mortality reported in White vs minority childhood CNS tumour patients.

Added value of this study

This registry-based retrospective cohort study complements previous research in three ways. First, cause-specific death was used as the outcome: cancer causes and non-cancer causes. Comprehensive studies of causes of death helped provide information on potential racial/ethnic disparities in cause-specific mortality, and further guide preventive measures to reduce racial/ethnic disparities on outcomes. Second, this study provided a preliminary picture and explanation of the long-term trends in racial/ethnic disparities. Finally, this study analysed the contribution of factors of racial/ethnic disparities in death, by using mediation analyses with variables from one large US national databases, including clinical and demographic factors as well as treatment factors. These findings added perspectives not considered in previous studies and provide valuable clues to reducing health disparities.

Implications of all the available evidence

We identified significant racial/ethnic disparities in children with malignant CNS tumours, with racial/ethnic minority patients consistently having higher risk of all-cause and cause-specific death than White patients. Although racial/ethnic disparities in death have reduced over the observation period, health inequities persist. In particular, the risk of death for Black patients remained higher than that for White patients after adjustment for factors in the mediation analysis model. Access to chemotherapy and radiotherapy were the important influential factors. Therefore, providing all people with the quality health care they need will help improve health equity.

Introduction

Central nervous system (CNS) tumours are one of the most common types of paediatric cancer, with approximately 6.2 per 100,000 children diagnosed.[1] With advances in neurosurgical techniques, radiotherapy, and combination chemotherapy, five-year relative survival for children with CNS malignant tumours has increased between 1975 to 1977 and 2009 to 2015 from approximately 58%–77%.[2–4] However, racial/ethnic disparities exist in the incidence and survival of childhood CNS tumours in the United States (US).[5] Compared with non-Hispanic White children, children from other minority ethnic background have a lower incidence rate of CNS tumours, but have a higher mortality rate.[1,6–14] In addition, survivors of CNS tumours face an increased risk of late death and a second tumour, but little is known about the disparity in cause-specific death among different racial/ethnic patients.[15–21] Thus, the focus of assessing health disparities in childhood patients with CNS tumours has shifted to disparities in death, especially for cause-specific death. A better understanding of cause-specific death in children with CNS tumours would be clinically useful, as it would help to hypothesise strategies for prevention and early intervention.

Various factors are thought to contribute to racial/ethnic disparities in death among children with tumours, including tumour characteristics,[4,13,22,23] access to health care,[24–30] socioeconomic status (SES),[22,31–34] bias among health care providers,[35] and late diagnosis.[36,37] Black children are more likely to have anaplastic astrocytomas and glioblastomas, and have a higher risk of death than White children.[9] Differences in health care influence racial/ethnic survival disparities.[26] Black children have the largest proportion of patients who received no form of surgical therapy/surgery status unknown.[9,38] If given equal access to treatment, Black children have similar survival rates to White children.[22,39] This suggests that equal health care may reduce or eliminate racial/ethnic disparities on death in childhood patients.[34] In addition, the influence of economic and social determinants on racial/ethnic disparities is gradually being emphasised. More than half of Hispanic and Black children are in low SES,[39] and they have a higher risk of death than White children.[34,40] This not only highlights an SES inequality that needs attention, but may suggest that it is possible to improve childhood patient survival by eliminating this potential disparity. In addition, one study found poor communication quality between clinicians and patients due to implicit racial bias among healthcare providers.[35] The implicit bias may result in patients and parents not accurately understanding treatment plans.[35] Racial/ethnic minority patients are more likely than White patients to assess to the emergency department, which can lead to a delayed diagnosis.[36,37,41] The above evidence indicates that understanding the underlying causes of racial/ethnic disparities is critical to reducing the risk of death.

More recently, attention has focused on the racial/ethnic disparities in death among children with CNS

tumours.[5,9,11,13,22,26,31,33,35,38,42] However, few studies have reported trends in racial/ethnic disparities in risk of all-cause and cause-specific death in children with malignant CNS tumours, and the underlying factors are not well understood. This study examined the trends of racial/ethnic disparities in death using data from the Surveillance, Epidemiology, and End Results (SEER) of children with malignant CNS tumours diagnosed from 2001 to 2020. Considering underlying factors that may influence on racial/ethnic disparities, we quantified a range of mediating factors, including tumour, treatment and socioeconomic factors. Assessing racial/ethnic disparities influenced on these factors would be beneficial in improving survival and promoting health equity.

Methods

SEER database and case selection

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[43] In this retrospective cohort analysis, we obtained participants using the SEER 17 from 2000 to 2020. Data were retrieved from 17 registries (San Francisco–Oakland SMSA, San Jose–Monterey, Connecticut, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta [Metropolitan], Los Angeles, Alaska Natives, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, Greater Georgia). SEER Registry 17 collected incidence, survival, and surgical treatment data of cancer, population-based cancer registries covering approximately 26.5% of the U.S. population (based on 2020 census). We included children diagnosed with primary CNS tumour types with malignant behaviour between 2001 and 2020, and we determined tumours using the *International Classification of Diseases for Oncology, Version 3 (ICD-O-3)* codes: C70.0-C70.9, C71.0-C71.9, C72.0-C72.9, C75.1, and C75.3. Only patients within the age range of 0–19 years were included. Of all patients who included for the study, 46 (0.3%) patients were excluded due to their tumours being initially identified by only autopsy or death certificate, and 141 (0.9%) patients were excluded due to their race/ethnicity being unknown (Text S2 and eFigure 1 in Supplementary Appendix).

Ethics

Given these data were collected as part of routine public health surveillance, written informed consent and ethical approval was exempt.

Covariates

Factors were extracted from the SEER database included race/ethnicity, age at diagnosis, sex, year of diagnosis, tumour factors (histological classification, stage at diagnosis and tumour grade), treatment factors (recommendations for surgical resection, cancer-directed surgery status, radiotherapy status and chemotherapy status) and socioeconomic factors (county of residence at diagnosis and median household income). Data on race/ethnicity were originally collected from the hospital reports, medical records, pathology reports, hospital discharge data, and death certificates, and submitted to regional or state cancer registries.[44] These data from such disparate sources (patient self-report, observing patient's physical appearance, or inferred from last names) were grouped into race and origin recode using specific algorithms by SEER.[45] We included children of non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander (API), non-Hispanic American Indian/Alaska Native (AI/AN), and Hispanic (all race). Patients were categorised into five age groups: <1, 1–4, 5–9, 10–14, and 15–19 years, according to the classification from the Central Brain Tumour Registry of the United States (CBTRUS).[1] Based on International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) code in SEER and the definitions from the CBTRUS, histological type were grouped into astrocytoma, gliomas, embryonal tumours, and other tumour types (eTable 1 in Supplementary Appendix).[1] Tumour grade was defined as low-grade (well-differentiated: Grade I; moderately-differentiated: Grade II) and high-grade (poorly-differentiated: Grade III; undifferentiated: Grade IV) tumour. We used "SEER historic stage A (1973–2015)" and "Combined Summary Stage (2004+)" to group stage at diagnosis into non-metastatic (localised/regional stage) and metastatic cancer (distant stage) cancer. Based on previous studies, we included the recommendations for surgical resection ("yes" or "no").[46] In addition, treatment factors including cancer-directed surgery, radiotherapy, and chemotherapy status were simply defined as "yes" and "no". In order to classify urban or rural patients, we used the Rural-Urban Continuum Code (RUCC) in 2013, which categorised patients in counties with codes 1–3 as urban and those in counties with codes 4–9 as rural.[47]

Outcomes

The follow-up of the patients was from the date of malignant CNS tumours diagnosis until the date of the outcome (that is, death), censored or the end of the study (that is, 31 December 2020), whichever occurred first. The outcomes of interest were all-cause and cause-specific death. All-cause death means death due to any cause. Cause-specific death classification was identified according to ICD-9 and ICD-10 in SEER, respectively. It can reflect the influence of medical technology, lifestyle and many other factors.[48] We classified cause-specific death into cancer-cause (including death due to CNS tumours and other cancers) and non-cancer-cause death (including death due to cardiovascular disease [CVD] and other non-cancer-cause death). All causes of death were independent. See eTable 2 in the Supplementary Appendix for the groups and ICD codes.

Statistics

Considering the competitive risk of death, we used the Fine and Gray models (function cuminc in R package 'tidycmprsk') to calculate the cumulative incidence of death, including overall, and stratified by race/ethnicity and diagnostic period.[49,50] We divided the year of diagnosis into four periods: 2001–2005, 2006–2010, 2011–2015, and 2016–2020. We limited the sample to patients diagnosed until 2016 for estimating the cumulative incidence of death at 5 years of follow-up.

The absolute racial/ethnic disparities were quantified using absolute rate difference in 5-year cumulative incidence of death between the period 2001–2005 and the period 2011–2015. To quantify the relative disparities, we used the cause-specific Cox proportional hazards regression to estimate adjusted hazard ratios (HR) with 95% confidence intervals (CI), adjusting for age as a categorical variable (R package 'survival'). We marked unknown data on these factors as unknown, and then included them in the Cox regression models as nominal variables. White patients were considered the reference group because they were the majority population. We first analysed all-causes of death as an outcome, and then analysed each specific cause, separately. We assessed the trend for relative disparities via including a multiplicative interaction term between race/ethnicity and diagnostic period in Cox regression models, and examined the Wald χ^2 (interaction terms were statistically significant, $P < 0.05$). Proportionality of hazards for key covariables was inspected by examining the correlation between time and scaled Schoenfeld residuals (function cox.zph in R package 'survival') (Text S1 and eFigure 2 in Supplementary Appendix). Given the assumption of proportional hazards was violated for age, we tested the relative disparities stratified by age in Cox regression model.

To further assess the contribution of factors to the racial/ethnic disparity in death, we used mediation analyses by Cox regression models.[51] Based on previous reports, we identified factors that were associated with racial/ethnic disparities, including tumour, treatment, and socioeconomic factors.[26,31] We conducted a univariate analysis to determine associations between these factors and outcomes, and the factor that was associated with outcome was included in mediation analyses.[52] In subsequent analyses, the analysis of comparing three racial/ethnic minorities patients (Black, Hispanic, and API) with White patients would be treated as three Cox regression models, and the contribution of factor would be calculated in each model. The baseline model in mediation analysis was defined as race/ethnicity plus age. Initially, each factor was separately included in the baseline model (race/ethnicity plus age plus one covariate), to calculate the racial/ethnic disparity HR between racial/ethnic minorities patients and White patients (defined as HR_A), and then ranked the HR_A from largest to smallest. Subsequently, factors were included in the baseline model sequentially in order of the decreasing HR_A (race/ethnicity plus age plus covariable one by one), to calculate the racial/ethnic disparity HR (defined as HR_B). Ultimately, the contribution of factors was calculated by $(D_- - D_+ \div D_0) \times 100$, where D_0 indicated racial/ethnic disparity HR from the baseline model, D_- was the HR_B from the model without the factor of interest, and D_+ was the HR_B from the model with the factor of interest. D was independent of which group was selected as the reference group.[51] To quantify racial/ethnic disparities in death among patients undergoing different treatments, we conducted subgroup analyses using Cox regression models. The Cox regression model controlled for histological type, stage at diagnosis, tumour grade and age. We further presented the distribution of factors by diagnostic period.

We conducted a series of sensitivity analyses. Because the treatment modality was associated with the tumour type, the new baseline model adjusted for tumour factors, race/ethnicity and age. The contribution of treatment factors to racial/ethnic disparities in death was recalculated. In addition, in previous mediation analyses, the contribution of factors to racial/ethnic disparities in death could be impacted on the order in which the factors were included in the model. This prompted us not to focus on the order in which the factors were included in the mediation analysis, and the contribution of each factor was individually calculated in the baseline model: race/ethnicity plus age plus one covariable. At this point, the contribution of each factor was defined by $(D_0 - D_+ \div D_0) \times 100$, where D_0 indicated racial/ethnic disparity HR from the baseline model, and D_+ was the HR from the baseline model with one factor of interest. We further utilised the Shapley Additive Explanations (SHAP) method to analyse the influence of individual factors, and visualise an individual's Shapley values.[53]

P values in Cox proportional risk regression model was using the Benjamini-Hochberg (BH) method for false discovery rate (FDR) control at level 0.05.[54] We used R software (version 4.2.0) and GraphPad Prism (version 8.0) for all analyses and visualisations.

Role of the funding source

The funder of the study had no role in study design, data analysis, data interpretation, manuscript preparation, and the decision to submit for publication. All authors approved the final manuscript for publication.

Results

Using SEER data among patients diagnosed from 2001 to 2020, there were 14 510 childhood malignant CNS tumour cases, including race/ethnicity of the White (8037 [55.4%]), Black (1530 [10.5%]), Hispanic (3697 [25.5%]), API (1131 [7.8%]) and AI/AN (115 [0.8%]). The mean age was 8.5 years (standard deviation [SD] 5.7), and 7988 (55.1%) were male patients. Overall, 26.9% (3908) of patients with CNS tumours died, including

20.4% (2955) from CNS tumours and 6.6% (953) from causes other than CNS tumours. The most common histological type was astrocytoma (5451 [37.6%]). Black patients had the lowest proportion of access to cancer-directed surgery (66.8%), and API patients had the highest proportion of access to chemotherapy (53.9%) and radiotherapy (48.6%) (Table 1). In the subsequent analysis, AI/AN patient (115 [0.8%]) and patients who died from unknown cause (83 [0.6%]) were excluded due to extremely small population size. Due to the same reason, patients who died from CVD (20 [0.1%]) were assigned to the group of deaths from other non-cancers.

Cumulative incidence of death in childhood malignant CNS tumours

The cumulative incidence of all-cause and cause-specific death is presented in eTable 3 in Supplementary Appendix. Compared with White patients, Black, Hispanic, and API patients always had a higher cumulative incidence of all-cause and cause-specific death. Black patients had the highest 5-year cumulative incidence of all-cause and cause-specific death. Trends in 5-year cumulative incidence of all-cause and cause-specific death among all patients and stratified by race/ethnicity were shown in Fig. 1, eTable 4 in the Supplementary Appendix. Between 2001 and 2015, the 5-year cumulative incidence of death from CNS tumours decreased across four race/ethnicity groups. The absolute change in the 5-year cumulative incidence of death from CNS tumours was largest for Black patients (–11.0 percentage points [ppt]), followed by API patients (–8.5 ppt). The 5-year cumulative incidence of death from other cancer increased across four race/ethnicity groups, with the largest absolute change in API (3.5 ppt) patients.

Absolute and relative racial/ethnic disparities in childhood malignant CNS tumours

The trends of absolute and relative racial/ethnic disparities over time were presented in Table 2. The absolute disparity in the 5-year cumulative incidence of death from CNS tumours between Black and White patients decreased from 11.8 ppt in 2001–2005 to 4.3 ppt in 2011–2015. Between API and White patients, the absolute disparity in death from CNS tumours decreased from 10.1 ppt in 2001–2005 to 5.1 ppt in 2011–2015. The absolute disparity in all-cause death between Hispanic and White patients slightly increased from 8.2 ppt in 2001–2005 to 9.4 ppt in 2011–2015. For relative disparities, the adjusted HR of death from CNS tumours between Hispanic and White patients increased from 1.33 (1.15–1.55) to 1.78 (1.44–2.20).

Mediation analysis of the racial/ethnic disparity in childhood malignant CNS tumours

In the univariate analyses, histological type, stage at diagnosis, tumour grade, recommendations for surgical resection, cancer-directed surgery, radiotherapy, and chemotherapy were associated with outcomes (eTable 5 in Supplementary Appendix). The Fig. 2 and eTable 6 in Supplementary Appendix presented racial/ethnic disparity HR after adjusting for factors. We further calculated the contribution of factors (Table 3). Access to radiotherapy, and chemotherapy together accounted for 5.3% of the disparity in death from CNS tumours between Black patients and White patients, accounted for 11.4% of the disparity between Hispanic patients and White patients, and accounted for 12.7% of the disparity between API patients and White patients.

In subgroup analyses, the risk of death from CNS tumours decreased for racial/ethnic minority patients undergoing treatment. Racial/ethnic disparity in death from CNS tumour narrowed between API patients undergoing radiotherapy and chemotherapy and White patients (eTable 7 in Supplementary Appendix). Since racial/ethnic disparities in death contributed by the tumour and treatment factors, we further presented the distribution of these factors by race/ethnicity and period of diagnosis (eFigure 3 in Supplementary Appendix). The proportion of API patients undergoing surgery (from 67.2% to 74.6%), chemotherapy (from 49.8% to 60.2%) and radiotherapy (from 49.0% to 51.8%) increased from 2001 to 2020. The proportion of Hispanic patients undergoing surgery (from 76.4% to 70.0%) decreased from 2001 to 2020. The proportion of Black patients undergoing surgery was lower than that of White patients between 2001 and 2005, and nearly the same as the proportion of White patients undergoing surgery between 2016 and 2020.

The contribution of each treatment factor to disparity in death was shown in eTable 8 in Supplementary Appendix. Access to radiotherapy, and chemotherapy together accounted for 5.2% of the disparity in death from CNS tumours between Black and White patients, accounted for 11.3% of the disparity between Hispanic and White patients, and accounted for 12.8% of the disparity between API and White patients. In addition, the contribution of each factor individually to racial/ethnic disparity in death was shown in eTable 9 in Supplementary Appendix. Access to radiotherapy and chemotherapy were the most influential factors to racial/ethnic disparity in death from CNS tumour death. The contribution of each factor to the all-cause and cause-specific death using the SHAP values, and access to radiotherapy was the largest contributor to the death from CNS tumour (eFigure 4 in Supplementary Appendix).

Discussion

In this study, we used SEER data to quantify racial/ethnic disparities in all-cause and cause-specific death among White, Black, Hispanic, and API children with malignant CNS tumours. We found that racial/ethnic minority patients with malignant CNS tumours had a poorer prognosis compared to White patients. The

	Overall (N = 14,510)	White (N = 8037)	Black (N = 1530)	Hispanic (N = 3697)	API (N = 1131)	AI/AN (N = 115)
Median follow-up (mo) (IQR)	70 (18, 145)	81 (24, 154)	58 (15, 129)	55 (14, 135)	55 (14, 130)	68 (21, 142)
Diagnostic year, n (%)						
2001–2005	3576 (2.46)	2055 (2.56)	369 (24.1)	872 (23.6)	253 (22.4)	27 (23.5)
2006–2010	3736 (25.7)	2123 (26.4)	381 (24.9)	931 (25.2)	275 (24.3)	26 (22.6)
2011–2015	3769 (26.0)	2065 (25.7)	405 (26.5)	964 (26.1)	304 (26.9)	31 (27.0)
2016–2020	3429 (23.6)	1794 (22.3)	375 (24.5)	930 (25.2)	299 (26.4)	31 (27.0)
Vital status, n (%)						
Alive	10,602 (73.1)	6162 (76.7)	1019 (66.6)	2541 (68.7)	796 (70.4)	84 (73.0)
CNS tumour	2955 (20.4)	1430 (17.8)	368 (24.1)	877 (23.7)	263 (23.3)	17 (14.8)
Other cancer	642 (4.4)	304 (3.8)	89 (5.8)	189 (5.1)	51 (4.5)	9 (7.8)
Other non-cancer	208 (1.4)	103 (1.3)	34 (2.2)	56 (1.5)	10 (0.9)	5 (4.3)
CVD	20 (0.1)	10 (0.1)	5 (0.3)	5 (0.1)	0 (0)	0 (0)
Unknown	83 (0.6)	28 (0.3)	15 (1.0)	29 (0.8)	11 (1.0)	0 (0)
Age at diagnosis (y), n (%)						
Mean (SD)	8.5 (5.7)	8.7 (5.7)	8.4 (5.6)	8.0 (5.6)	8.8 (5.8)	8.6 (5.8)
<1	809 (5.6)	402 (5.0)	93 (6.1)	237 (6.4)	73 (6.5)	4 (3.5)
1–4	3712 (25.6)	2004 (24.9)	388 (25.4)	1017 (27.5)	268 (23.7)	35 (30.4)
5–9	3849 (26.5)	2096 (26.1)	413 (27.0)	1034 (28.0)	279 (24.7)	27 (23.5)
10–14	3350 (23.1)	1919 (23.9)	350 (22.9)	790 (21.4)	266 (23.5)	25 (21.7)
15–19	2790 (19.2)	1616 (20.1)	286 (18.7)	619 (16.7)	245 (21.7)	24 (20.9)
Sex, n (%)						
Male	7988 (55.1)	4462 (55.5)	784 (51.2)	2039 (55.2)	642 (56.8)	61 (53.0)
Female	6522 (44.9)	3575 (44.5)	746 (48.8)	1658 (44.8)	489 (43.2)	54 (47.0)
Stage at diagnosis, n (%)						
Localised/regional	922 (6.4)	486 (6.0)	98 (6.4)	256 (6.9)	77 (6.8)	5 (4.3)
Distant	12 806 (88.3)	7120 (88.6)	1327 (86.7)	3257 (88.1)	998 (88.2)	104 (90.4)
Unknown	782 (5.4)	431 (5.4)	105 (6.9)	184 (5.0)	56 (5.0)	6 (5.2)
Tumour grade, n (%)						
Low-grade	1520 (10.5)	878 (10.9)	169 (11.0)	363 (9.8)	93 (8.2)	17 (14.8)
High-grade	1939 (13.4)	989 (12.3)	212 (13.9)	571 (15.4)	152 (13.4)	15 (13.0)
Unknown	11,051 (76.2)	6170 (76.8)	1149 (75.1)	2763 (74.7)	886 (78.3)	83 (72.2)
Histological type, n (%)						
Astrocytoma	5451 (37.6)	3269 (40.7)	544 (35.6)	1286 (34.8)	309 (27.3)	43 (37.4)
Gliomas	3550 (24.5)	2012 (25.0)	419 (27.4)	813 (22.0)	273 (24.1)	33 (28.7)
Embryonal	1050 (7.2)	508 (6.3)	120 (7.8)	339 (9.2)	77 (6.8)	6 (5.2)
Other	4459 (30.7)	2248 (28.0)	447 (29.2)	1259 (34.1)	472 (41.7)	33 (28.7)
Surgery, n (%)						
Yes	10,100 (69.6)	5575 (69.4)	1022 (66.8)	2647 (71.6)	777 (68.7)	79 (68.7)
No/Unknown	4410 (30.4)	2462 (30.6)	508 (33.2)	1050 (28.4)	354 (31.3)	36 (31.3)
Recommendations for surgical resection, n (%)						
Yes	10,301 (71.0)	5687 (70.8)	1048 (68.5)	2693 (72.8)	791 (69.9)	82 (71.3)
No	4141 (28.5)	2304 (28.7)	473 (30.9)	994 (26.9)	338 (29.9)	32 (27.8)
Unknown	68 (0.5)	46 (0.6)	9 (0.6)	10 (0.3)	2 (0.2)	1 (0.9)
Radiotherapy, n (%)						
Yes	5589 (38.5)	2809 (35.0)	605 (39.5)	1586 (42.9)	550 (48.6)	39 (33.9)
No/Unknown	8921 (61.5)	5228 (65.0)	925 (60.5)	2111 (57.1)	581 (51.4)	76 (66.1)
Chemotherapy, n (%)						
Yes	6300 (43.4)	3238 (40.3)	634 (41.4)	1774 (48.0)	610 (53.9)	44 (38.3)
No/Unknown	8210 (56.6)	4799 (59.7)	896 (58.6)	1923 (52.0)	521 (46.1)	71 (61.7)
Median household income, n (%)						
<$59,999	3164 (21.8)	1925 (24.0)	531 (34.7)	602 (16.3)	65 (5.7)	41 (35.7)
$60,000–$74,999	5261 (36.3)	2612 (32.5)	561 (36.7)	1708 (46.2)	364 (32.2)	16 (13.9)
$75,000+	6081 (41.9)	3499 (43.5)	438 (28.6)	1386 (37.5)	701 (62.0)	57 (49.6)

(Table 1 continues on next page)

	Overall (N = 14,510)	White (N = 8037)	Black (N = 1530)	Hispanic (N = 3697)	API (N = 1131)	AI/AN (N = 115)
(Continued from previous page)						
Unknown	4 (0)	1 (0)	0 (0)	1 (0)	1 (0.1)	1 (0.9)
County of residence at diagnosis, n (%)						
Urban	13,068 (90.1)	6924 (86.2)	1406 (91.9)	3569 (96.5)	1100 (97.3)	69 (60.0)
Rural	1408 (9.7)	1112 (13.8)	124 (8.1)	127 (3.4)	30 (2.7)	15 (13.0)
Unknown	34 (0.2)	1 (0)	0 (0)	1 (0)	1 (0.1)	31 (27.0)

Abbreviation: API, Asian or Pacific Islander, non-Hispanic Asian/Pacific Islander; AI/AN, American Indian/Alaska Native; IQR, interquartile range; SD, standard deviation; CVD, cardiovascular disease; CNS, central nervous system.

Table 1: **Summary of population characteristics of childhood malignant CNS tumours stratified by race/ethnicity, Surveillance, Epidemiology, and End Results data among patients diagnosed years 2001–2020.**

absolute disparities in CNS tumour death narrowed between Black and White patients, and narrowed between API patients and White patients, while the relative disparities between Hispanic and White patients widened from 2001 to 2020. With mediation analysis, we further found that access to treatment after diagnosis had a slightly contribution on racial/ethnic disparities in death from CNS tumour. Our study could provide a direction to address racial/ethnic disparities in death among childhood malignant CNS tumours.

Our study found that the 5-year cumulative incidence of all-cause death and death from CNS tumour among children with malignant CNS tumours decreased significantly from 2001–2005 to 2011–2015. However, this benefit had not reached all racial/ethnic patients equally, and racial/ethnic minority patients remained at a higher 5-year cumulative incidence of all-cause death and death from CNS tumour than White patients, consistently. Racial/ethnic minority patients were usually in lower SES, they were at high risk of death.[32,35,55,56] Previous studies have reported that SES mediated racial/ethnic survival disparities in childhood cancer patients, but they found no significant evidence that SES mediated disparities in children with CNS tumours.[31] Since SES in the SEER database was an ecological variable, differences in an individual's education, income, and occupation could not be detected. Therefore, the error in this factor might make its contribution to the disparity underestimated.[57] In this study, we considered the contribution of county of residence at diagnosis and median household income to racial/ethnic disparities in death, however, the associations between these factors and death were not significant. Thus, these factors were not included in the mediation analysis. However, it should be interpreted with caution because the income is at area level, and so although we didn't find an association between area level SES and outcome does not mean that there isn't an

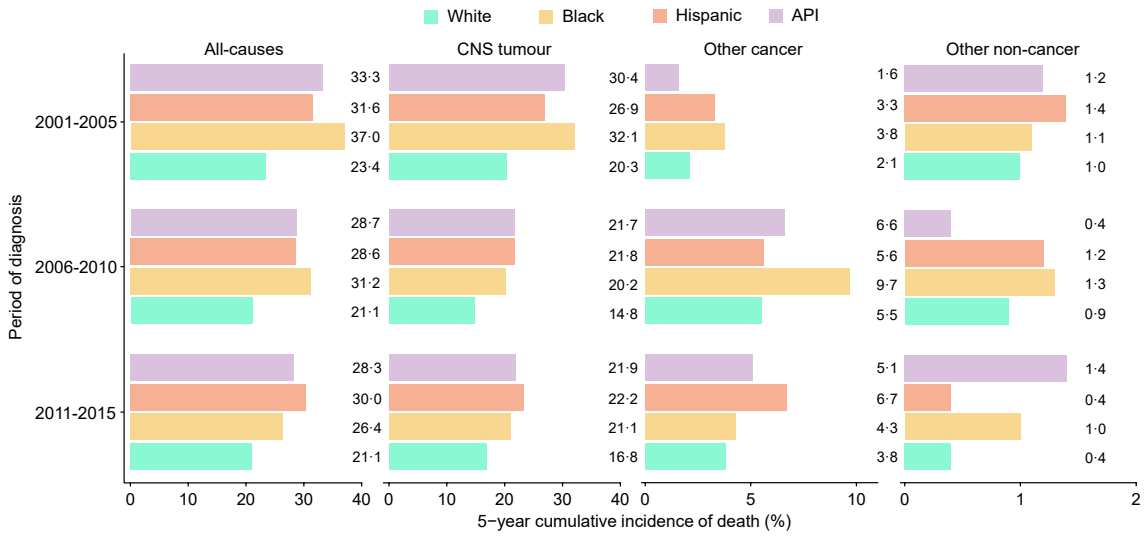

Fig. 1: 5-year cumulative incidence of all-cause and cause-specific death in children with malignant CNS tumours by race/ethnicity and diagnostic period. Abbreviations: API, Asian or Pacific Islander, non-Hispanic Asian/Pacific Islander; CNS, central nervous system.

	All-causes[a]		CNS tumour[a]		Other cancer[a]		Other non-cancer[a]	
	HR (95%CI)	Absolute disparity (ppt)[b]	HR (95%CI)	Absolute disparity (ppt)[b]	HR (95%CI)	Absolute disparity (ppt)[b]	HR (95%CI)	Absolute disparity (ppt)[b]
Black vs White								
2001–2020	1.52 (1.38–1.68)	9.6	1.47 (1.31–1.64)	7.0	1.62 (1.28–2.05)	2.1	1.96 (1.33–2.89)	0.4
2001–2005	1.69 (1.42–2.01)	13.6	1.60 (1.32–1.94)	11.8	2.18 (1.29–3.69)	1.7	2.14 (1.17–3.93)	0.1
2006–2010	1.61 (1.33–1.95)	10.1	1.47 (1.16–1.86)	10.1	1.92 (1.34–2.73)	4.2	1.97 (0.97–4.01)	0.4
2011–2015	1.23 (0.99–1.51)	5.4	1.25 (0.98–1.58)	4.3	1.14 (0.68–1.91)	0.5	1.25 (0.47–3.35)	0.6
2016–2020	1.59 (1.23–2.04)	–	1.58 (1.20–2.10)	–	1.30 (0.68–2.47)	–	3.28 (1.07–10.07)	–
P for trend[c]	0.17	–	0.30	–	0.19	–	0.84	–
Hispanic vs White								
2001–2020	1.45 (1.35–1.57)	8.4	1.47 (1.35–1.59)	6.6	1.42 (1.18–1.70)	1.5	1.37 (0.99–1.90)	0.2
2001–2005	1.32 (1.16–1.52)	8.2	1.33 (1.15–1.55)	6.6	1.31 (0.83–2.07)	1.2	1.21 (0.70–2.09)	0.4
2006–2010	1.38 (1.19–1.59)	7.5	1.49 (1.26–1.77)	7.0	1.07 (0.78–1.46)	0.1	1.30 (0.72–2.34)	0.3
2011–2015	1.48 (1.28–1.71)	9.4	1.43 (1.21–1.69)	6.4	1.83 (1.32–2.53)	2.9	0.97 (0.43–2.22)	0
2016–2020	1.84 (1.53–2.22)	–	1.78 (1.44–2.20)	–	1.83 (1.19–2.83)	–	3.36 (1.37–8.25)	–
P for trend[c]	<0.0001	–	<0.0001	–	0.11	–	0.14	–
API vs White								
2001–2020	1.37 (1.22–1.54)	8.2	1.44 (1.26–1.64)	7.1	1.25 (0.93–1.69)	0.8	0.78 (0.41–1.49)	0.2
2001–2005	1.37 (1.10–1.70)	9.9	1.47 (1.16–1.85)	10.1	0.81 (0.32–2.03)	−0.5	0.85 (0.31–2.38)	0.2
2006–2010	1.42 (1.13–1.77)	7.6	1.58 (1.22–2.05)	6.9	1.25 (0.78–2.00)	1.1	0.25 (0.03–1.82)	−0.5
2011–2015	1.43 (1.14–1.79)	7.3	1.42 (1.10–1.83)	5.1	1.44 (0.84–2.47)	1.3	1.43 (0.49–4.19)	1.0
2016–2020	1.28 (0.94–1.73)	–	1.28 (0.91–1.80)	–	1.34 (0.68–2.67)	–	0.77 (0.10–6.19)	–
P for trend[c]	0.98	–	0.64	–	0.58	–	0.54	–

Abbreviation: CI, confidence interval; HR, hazard ratio; API, Asian or Pacific Islander, non-Hispanic Asian/Pacific Islander; CNS, central nervous system; US, United States; ppt, percentage points. [a]The Cox regression models were adjusted for age as a categorical variable (<1, 1–4, 5–9, 10–14,15–19 years). [b]The trend of absolute disparities for the 5-year cumulative incidence of death was calculated using White patients as the reference category. [c]P for trend values were calculated by the interaction term between race/ethnicity and diagnostic period in regression models.

***Table 2*: Adjusted HR and unadjusted absolute disparities for all-cause and cause-specific death in black, Hispanic, and API children with malignant CNS tumours compared with White patients in the US, 2001–2020.**

association between individual SES and outcome. Future studies could quantify the contribution of SES to racial/ethnic disparities in death among children with malignant CNS tumours from multiple perspectives.

Advances in multimodal therapy have significantly improved the survival of children with CNS tumours.[58,59] Our study found that access to chemotherapy and radiotherapy, an integral part of managing CNS tumours, mediated the racial/ethnic disparities in death. Access to treatment was itself influenced by a myriad of factors, which included health insurance and SES. Individuals without private insurance and those with lower SES might not access to more comprehensive treatment.[30,42,60] Racial/ethnic minority patients generally had low SES, and the proportion of individuals with private insurance was lower than that of White patients.[27,61–63] Differences in these factors might be responsible for the lack of access to quality care, which contributed to a high risk of death for racial/ethnic minority patients. A previous study evaluated racial/ethnic survival disparities among children with tumours at the SEER and St Jude Children's Research Hospital from 1992 to 2007.[64] In the SEER, Black children with astrocytomas and ventricular meningiomas experienced little improvement in survival. However, the survival rate for Black children improved significantly, even surpassed that of White patients during the period 2001–2007 at St. Jude Children's Research Hospital, where patients were accepted without regard to race/ethnicity, insurance status, or economic status. These allowed them to receive equal and comprehensive treatment. Another study found that controlling for treatment and SES, the risk of death decreased for Black children with CNS tumours, and the disparity in death was no longer significant between them and White patients with the same localised/metastatic tumour.[22] We observed that the risk of death for Black patients had decreased, and the proportion of Black patients undergoing surgery was gradually close to that of White patients from 2001–2005 to 2015–2020. The disparity in death from CNS tumours between Black and White patients was the smallest during the period 2011–2015, when the proportion of access to radiotherapy and chemotherapy was closest between the two groups of patients. Nonetheless, this did not mean that Black patients after diagnosis will access to comprehensive care in a timely manner.

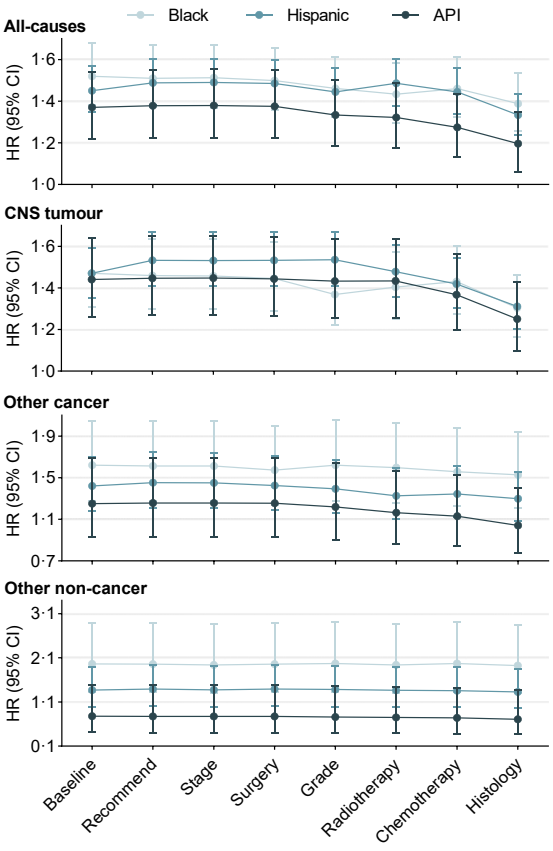

Fig. 2: Adjusted HR with 95%CI for all-cause and cause-specific deaths among Black, Hispanic, and API patients compared to White patients after controlling for factors that contribute the disparities. Factors were included in the baseline model sequentially in order of the decreasing HR_A. Factor axis used the order of variables for mediation analyses in API vs White patients. Abbreviations: API, Asian or Pacific Islander, non-Hispanic Asian/Pacific Islander; CNS, central nervous system; CI, confidence interval; HR, hazard ratio.

Currently, a large number of studies in adults report that delaying cancer treatment results in decreased patient survival.[65] A study analysing postoperative radiotherapy patterns of care in medulloblastoma patients aged 3–8 years showed that delayed postoperative radiotherapy was associated with poorer survival in this age group.[66] Magnetic resonance imaging (MRI) was an enhanced diagnostic tool to guide the radiotherapy pattern of patients.[67] Missed MRI appointments might result in a delay in appropriate imaging, which might have a negative impact on results.[68] However, some studies have reported an increased likelihood of imaging missed care opportunities among Black children.[69,70] Therefore, at the end of this study, Black patients still had a higher risk of death than White patients although the disparity has narrowed. It might provide a basis to explain the narrower disparity in death between Black and White patients, i.e., that access to equal treatment would help decrease the risk of death for Black patients.

Many studies have reported that cancer patients who enter high-volume hospitals with a large number of neurosurgeons would have a better prognosis.[22,23,29] Hispanic children with CNS tumours were less likely to access to treatment in high-volume hospitals than White, Black, or Asian children from 1988 to 2005.[29] From 2016 to 2020, the proportion of Hispanic patients in high-volume hospitals remained lower than that of White patients.[71] Hispanic patients undergoing treatment using low-volume surgeons more frequently, with consistently poorer care.[42,71] In addition, one study reported that Hispanic patients were more likely to arrive at the hospital for craniotomy for brain tumours through emergency admissions, suggesting that they failed to access to adequate care when early symptoms first appeared.[42] Our study found that the proportion of Hispanic patients with metastatic tumour increased from 2006 to 2020, and higher than other racial/ethnic patients in the period 2016–2020. Meanwhile, Hispanic patients had a higher risk of death from CNS tumours than White patients, and the risk increased over time. This might be due to the failure of Hispanic patients to access to appropriate treatment and care in the early stages of the disease. Prior studies documented that exclusionary policies weaken Hispanic children's access to health care, which could be detrimental to children's health.[72,73] Hispanic children residing in states with higher levels of systemic inequity are more likely to experience chronic physical health conditions.[74] Therefore, addressing the effects of discriminatory policies and prejudiced social contexts on children's health, and increasing the proportion of Hispanic patients access high-quality care at large hospitals, would contribute to alleviating disparities in deaths among children with CNS tumours.

Our findings showed that the disparities in death from CNS tumours between API and White patients narrowed from 2001 to 2020. The proportion of API patients undergoing treatment increased during the observation period. In particular, during the period 2016–2020, the proportion of API patients undergoing treatment increased substantially, and the disparity in deaths from CNS tumours between API patients and White patients was no longer significant. This might indicate that comprehensive health care would reduce the risk of death for API patients. Notably, we found that the 5-year cumulative incidence of death from other cancers among API patients exhibited a slight upward trend from 2001 to 2020. Currently, the known evidences suggest that mutations in susceptibility genes are a possible cause of childhood multiple cancers.[75] Among patients with Li-Fraumeni syndrome caused by germline mutations in the TP53 tumour suppressor gene, children aged 0–19 years tended to be more susceptible to a variety of primary cancers, including brain

All-cause		CNS tumour		Other cancers		Other non-cancer	
Factors	Contribution, %[b]	Factors	Contribution, %[b]	Factors	Contribution, %[b]	Factors	Contribution, %[b]
Black vs White							
Recommend[c]	0.39	Recommend[c]	0.48	Grade	0.06	Grade	−0.54
Surgery	0.07	Surgery	0.14	Recommend[c]	0.55	Chemotherapy	0.21
Stage	0.93	Stage	0.82	Surgery	0	Recommend[c]	0.69
Grade	2.49	Chemotherapy	1.01	Chemotherapy	0.90	Surgery	0.03
Chemotherapy	0.02	Grade	1.82	Stage	1.55	Stage	0.77
Histology	1.81	Histology	2.43	Radiotherapy	0.88	Radiotherapy	0.10
Radiotherapy	2.99	Radiotherapy	4.32	Histology	1.84	Histology	0.57
Total, %[d]	8.70	Total, %[d]	11.02	Total, %[d]	5.78	Total, %[d]	1.84
Hispanic vs White							
Recommend[c]	−2.41	Histology	−4.78	Recommend[c]	−2.32	Recommend[c]	−1.81
Surgery	−0.14	Surgery	0.24	Surgery	0.12	Surgery	−0.11
Histology	0.30	Recommend[c]	−0.04	Stage	1.82	Grade	0.62
Stage	0.07	Stage	−0.02	Grade	2.28	Stage	0.88
Grade	2.79	Grade	3.71	Radiotherapy	3.46	Radiotherapy	0.80
Chemotherapy	0	Chemotherapy	4.06	Chemotherapy	1.25	Chemotherapy	0.46
Radiotherapy	7.62	Radiotherapy	7.36	Histology	1.93	Histology	2.11
Total, %[d]	8.24	Total, %[d]	10.53	Total, %[d]	8.54	Total, %[d]	2.95
API vs White							
Recommend[c]	−0.51	Recommend[c]	−0.56	Recommend[c]	−0.32	Recommend[c]	0.30
Surgery	−0.07	Surgery	−0.07	Surgery	0.08	Stage	0.22
Stage	0.26	Stage	0.28	Stage	0.15	Surgery	−0.10
Grade	3.03	Histology	0.70	Grade	3.00	Grade	1.91
Histology	0.90	Grade	−0.07	Chemotherapy	4.39	Radiotherapy	1.39
Chemotherapy	3.44	Chemotherapy	4.65	Radiotherapy	2.66	Chemotherapy	0.72
Radiotherapy	5.72	Radiotherapy	8.07	Histology	7.06	Histology	4.17
Total, %[d]	12.77	Total, %[d]	13.00	Total, %[d]	17.02	Total, %[d]	8.60
Other racial/ethnic minority patients vs White							
Recommend[c]	−1.37	Histology	−1.71	Recommend[c]	−1.32	Recommend[c]	−0.92
Surgery	0	Recommend[c]	0.10	Surgery	0.06	Surgery	0
Histology	1.68	Surgery	−0.03	Stage	1.40	Grade	0.64
Stage	−0.10	Stage	−0.13	Grade	2.08	Stage	0.68
Grade	2.12	Grade	2.87	Chemotherapy	2.74	Radiotherapy	0.63
Chemotherapy	2.43	Chemotherapy	3.26	Radiotherapy	1.61	Chemotherapy	0.35
Radiotherapy	4.69	Radiotherapy	6.72	Histology	2.93	Histology	0
Total, %[d]	9.43	Total, %[d]	11.07	Total, %[d]	9.49	Total, %[d]	1.37

Abbreviation: API, Asian or Pacific Islander, non-Hispanic Asian/Pacific Islander; CNS, central nervous system; US, United States. [a]The Cox regression models were adjusted for age as a categorical variable (<1, 1–4, 5–9, 10–14,15–19 years). Factors were included in the baseline model sequentially (race/ethnicity plus age plus covariable one by one) in order of the decreasing HR_A. If a variable was not significantly associated with an outcome in univariate analysis, it was not included in the mediation analysis. [b]Contribution of factors calculated by $(D_- - D_+ \div D_0) \times 100$. A negative contribution indicated an increase in racial/ethnic disparities when the covariable is added to the model. [c]Recommend means a recommendation for surgical resection. [d]Together, these factors contribute to racial/ethnic disparities in all-cause and cause-specific death.

Table 3: **Contribution of factors calculated by mediation analysis in the US, 2001–2020.**[a]

tumours.[76] Another study reported that cancer therapies might lead to multiple cancers.[75] Prolonged chemotherapy might have an influence on somatic TP53 mutations, and high-dose radiotherapy could also lead to the development of second cancers.[76–78] This suggested that focusing only on the changes in the measures of all-cause death might lead to the trends in some of the cause-specific deaths being overlooked. Management of tumours needed to consider other disease, such as second tumours. Distinguishing racial/ethnic disparities by cause of death provided more precise direction for management and prevention. In addition, attempted to consider the tumour genome during treatment could help quantify the type and dose of drugs and improve patient survival on an individual level.

This study differs from other survival analyses of childhood CNS tumours because it uses a population-based sample of the nationally representative data set and presents racial/ethnic disparities in all-cause and cause-specific deaths. For minimising disagreement

about disparity trends and improving the interpretability of the findings, we evaluated the trends of disparities during 2001–2020 using absolute and relative measures.[79] Mediation analysis was conducted to estimate the contribution of each factor to racial/ethnic disparities in death. We further systematically adjusted for tumour factors in the baseline model of mediation analysis, in order to rule out the influence of tumour factors on the choice of treatment. In addition, given that the original mediation analysis might be impacted on the order in which the variables were included in the model, we calculated the contribution of each variable to the racial/ethnic disparity in death individually, which improved the robustness of the results.

However, this study had some limitations. First, we could not rule out potential misclassification of cause of death and race/ethnicity in population-based tumour registries. However, in order to minimise this misclassification, patients with unknown causes of death and race/ethnicity were not be included in the study. Second, given the limited number of deaths in children with CNS tumours, the available data were insufficient to support an analysis of racial/ethnic disparities in deaths grouped by histologic type, and larger sample sizes could be used in the future to analyse racial/ethnic disparities in each histologic type. Third, we were unable to obtain individual-level SES data, such as household income and educational attainment, which limited our ability to further explore the influence of socioeconomic factors on racial/ethnic disparities in death among childhood CNS tumour patients. Fourth, lifestyle, psychological factors, and tumour biologic factors may influence racial/ethnic disparities.[80–82] However, these detailed data are not available.

In conclusion, in this study, the risk of death from CNS tumours among Black and API patients reduced between 2001 and 2020. The disparities in death from CNS tumour have narrowed between Black patients and White patients and between API patients and White patients. However, health inequalities between racial/ethnic minority patients and White patients persist. Access to high-quality health care can help reduce racial/ethnic disparities in death, but multifaceted research is still needed to explore the underlying factors contributed to unequal treatment among children with CNS tumours.

Contributors

BZ and HW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: HW, BY, TT, BZ. Acquisition, analysis, or interpretation of data: HW, TT, MG, YM, XW, Drafting of the manuscript: HW. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis: HW, MG, YM, BY. Obtained funding: BZ, XW. Administrative, technical, or material support: BZ, XW. Supervision: BY, TT, BZ, XW. All authors contributed to data interpretation and rewriting of the paper. All authors had full access to all the data. The corresponding authors were responsible for the decision to submit the manuscript. All authors read and approved the final version of the manuscript. HW, BZ and BY have verified the underlying data.

Data sharing statement

No additional data available. The data for this study were acquired by application to the restricted access National Cancer Database and the data use agreement does not allow data sharing.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102816.

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