Trends in childhood cancers at Tygerberg Hospital from 1994 to 2014

S Ndlovu,[1,3] MPhil (Cancer Science); **T M Esterhuizen**,[2] MSc (Epidemiol); **R Uys**,[1] MB ChB; **A van Zyl**,[1] FC Paed, Cert Med Oncol (Paed); **M Kruger**,[1] FC Paed (SA), PhD

[1] *Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa*

[2] *Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa*

[3] *African Cancer Institute, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa*

Corresponding author: *M Kruger (marianakruger@sun.ac.za)*

Background. There is a paucity of data regarding childhood cancer incidence in low- and middle-income countries owing to a lack of disease-specific, hospital- and population-based registries.
Objective. To describe the disease profile and outcome of children with cancer, treated at a single institution in South Africa between 1994 and 2014.
Methods. Data collected included demographic data (age at diagnosis, sex, stage or risk group, race) and 5-year overall survival (OS) of children aged ≤15 years diagnosed with cancer. Time to event and factors associated with 5-year outcomes were analysed, using Kaplan-Meier curves and Cox regression analysis.
Results. The most common malignancies were leukaemia (27.7%), brain tumours (18.4%), lymphomas (14.1%), nephroblastoma (8.0%) and soft-tissue sarcomas (7.4%) for 935 patient records. Limited-disease solid tumours and standard-risk haematological malignancies had good OS rates of 77.7% and 85.9%, respectively, although OS for the whole group was 60.2%. Nephroblastoma (89.3%), retinoblastoma (86.7%), Hodgkin's lymphoma (89.7%) and Burkitt lymphoma (75.5%) had the best OS. Type of cancer ($p<0.01$), solid-tumour stage ($p<0.001$) and risk classification for haematological malignancies ($p<0.001$) were significantly associated with mortality.
Conclusions. Underlying cancer diagnosis, stage and risk group remained significant factors influencing survival with good OS for limited disease in solid tumours and standard-risk haematological malignancies, which was comparable with survival rates in high-income countries.

S Afr J Child Health 2023;17(2):e1944. https://doi.org/10.7196/SAJCH.2023.v17i2.1944

Cancer is a leading cause of death in children globally and is ranked as the second most common cause of death in 5- to 14-year-old children in the USA after trauma.[1] Most childhood cancer deaths occur in low- and middle-income countries (LMICs).[2] International childhood cancer incidence rates increased during the 2001 - 2010 period compared with previously reported rates.[2] A baseline model created from the Surveillance, Epidemiology and End Results (SEER) Program in 2015 estimated a 4.5% increase.[3] The annual childhood cancer incidence for South Africa (SA) was 45 per million for the 1987 - 2007 period,[4] which was lower than the incidence reported in high-income countries (HICs), where it was estimated to be 137.5 (95% CI 136.7 - 138.3) per million person-years.[5] The lower incidence in SA may be due to a poor referral system, incorrect diagnosis or under-reporting. Survival in SA was estimated to be 52.1% for the period between 1987 and 2011,[6] which was low compared with HICs, where survival ranged between 78% and 83%.[7]

Most childhood cancers have no known cause. However, known risk factors include genetic (5 - 10%) or congenital disorders, as well as chronic infections. HIV, malaria and Epstein-Barr virus (EBV) are comorbidities that pose additional risk factors for childhood cancers in LMICs owing to their high prevalence.[8,9] SA has a large HIV burden and in 2012 the overall survival (OS) for children living with HIV (and on antiretroviral therapy (ART)) who were diagnosed with cancer was 57.8%.[10]

In 2018 the World Health Organization (WHO), in collaboration with the International Society of Pediatric Oncology (SIOP), launched a global initiative to prioritise childhood cancer and to improve global survival to 60% by 2030.[11] This necessitates the generation of local data regarding childhood cancer profiles and survival.[11] The aim of the present study was to determine the paediatric cancer disease profile, 5-year OS and to assess factors associated with 5-year mortality of children treated at Tygerberg Hospital between 1994 and 2014.

Methods

A descriptive cohort study was conducted. All children aged 0 - 15 years who were diagnosed with a malignancy between 1 January 1994 and 31 December 2014 at the Tygerberg Hospital Paediatric Oncology Unit (POU) in Cape Town, SA, were prospectively registered in the South African Children's Tumour Registry (SACTR). The list of patients was extracted from this registry and analysed retrospectively. Additional disease and outcome data were collected from patient files, as well as the hospital's online record system. Variables included demographic data (date of birth, sex, age at diagnosis, race), cancer diagnosis, stage or risk group, weight,

height, HIV status and comorbid diseases at diagnosis. Patients with HIV were included in this study but did not receive ART prior to 2004 in SA, therefore the level of immune suppression of these patients was likely more than those who received ART from 2004. Race was included as a variable because racial disparities have been documented in previous studies.[8,12,13] The end-point for follow-up data was 60 months post diagnosis. Patients who were lost to follow-up were included in the analysis as censored observations. As major changes related to policy and treatment protocols occurred in the healthcare system after 2001, the period was divided into two study periods for comparison: study period 1 (SP1) included patients diagnosed between 1994 and 2001; and study period 2 (SP2) included patients diagnosed between 2002 and 2014. Malignancies were classified according to diagnosis, while age was divided into 3 groups: 0 - 4; 5 - 9; and 10 - 15 years. Solid-tumour stage was documented according to the stage at diagnosis: stages 1 and 2 were classified as limited disease, while stages 3 and 4 were classified as advanced disease. Haematological malignancies were classified as either standard or high-risk. Leukaemia was stratified according to the standard international risk classification system using age, sex, white blood cell count, genetic subtypes and response to therapy as risk factors.[14,15] For lymphoma, stage 1 and 2 were classified as standard risk and stages 3 and 4 as high risk.[16]

WHO growth charts were used to define several nutritional parameters. Weight-for-length *Z*-scores for children under 5 years of age were interpreted as either obese (>3 standard deviation (SD)), overweight (>2 SD and ≤3 SD), normal (<2 SD and ≥–2 SD), wasted (<–2 SD and ≥–3 SD) or severely wasted (<-3 SD). Similarly, body mass index (BMI)-for-age *Z*-scores were used to define the nutritional status of children aged 5 - 15 years as obese (>3 SD), overweight (>2 SD and ≤3 SD), normal (≤2 SD and ≥-2 SD), wasted (<–2 SD and ≥–3 SD) and severely wasted (<–3 SD). Height-for-age *Z*-scores were interpreted as stunted (<–2 SD and ≥–3 SD), very stunted (<–3 SD) and normal (>–2) (WHO AnthroCalc; http://www.who.int/growthref/tools/en/). The associations between OS and sex, age, stage or risk group, comorbidities and nutritional status were investigated, as well as the disease profile and outcomes for the two study periods.

Statistical analysis was done using Stata (version 17; StataCorp., USA). A *p*-value <0.05 was considered statistically significant. Descriptive statistics were used to describe childhood cancer trends, demonstrating the frequency of the cancer types, distribution among sex, age groups and ethnic groups as racial differences may exist, especially in access to healthcare.[12]] Patients who were lost to follow-up within 5 years were treated as censored observations. Survival analysis was done using Kaplan-Meier survival curves. Log-rank tests were used to compare time to mortality between different factors. Factors that showed an association at $p<0.1$ were used as independent variables in a Cox proportional hazards regression model for time to mortality within 5 years. Independent variables with *p*-values <0.05 in the Cox proportional hazards regression model were considered statistically significant. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported.

Ethics approval was obtained from the Stellenbosch University Health Research Ethics Committee (ref. no. S19/10/208) and the Western Cape Provincial Health Research Committee granted permission to conduct the study at Tygerberg Hospital. A waiver of individual informed consent was obtained as the study posed minimal risk and used retrospective anonymised data. Initially, parents provided informed consent for their children's data to be documented in the SACTR. Further consent was obtained from the custodian of the data at Tygerberg Hospital and the local custodian of the SACTR to access the data.

Results

A total of 935 cases were included for data analysis, while 18 records were excluded owing to missing data or non-malignant diagnoses (Supplementary Fig. 1 (https://www.samedical.org/file/2030)). One hundred cases were excluded from a sub-analysis regarding stage and OS, while 161 cases were excluded from nutritional status analysis owing to missing data (Supplementary Fig. 1, https://www.samedical.org/file/2030).

The mean (range) number of patients diagnosed per year was 45 (31 - 60) with a median (interquartile (IQR)) age of 5 (2 - 9) years. The overall male-to-female ratio was 1.3:1, with an increased male-to-female ratio of 2:1 in lymphoma and 3.2:1 in T-cell acute lymphoblastic leukaemia (T-ALL). Most children (*n*=438; 46.8%) were in the 0 - 4 years age group, followed by those aged 5 - 9 years (*n*=279; 29.8%) and 10 - 15 years (*n*=218; 23.3%) (Supplementary Table 1, https://www.samedical.org/file/2032). Most children were coloured (also known as mixed race elsewhere),[17] (*n*=588; 62.9%), followed by black (*n*=188; 20.1%), white (*n*=156; 16.7%) and Indian (*n*=3; 0.3%) children (Supplementary Table 1, https://www.samedical.org/file/2032).

There were 544 (58.2%) solid tumours: *n*=197 (56.3%); and *n*=347 (59.3%) for SP1 and SP2, respectively. Most of the patients had advanced disease: 55.8% (*n*=110) and 49.9% (*n*=173), while 34.5% (*n*=68) and 30.8% (*n*=107) had limited disease and 9.6% (*n*=19) and 19.3% (*n*=67) had missing data in SP1 and SP2, respectively. There were 391 (41.8%) haematological malignancies: 43.7% (*n*=153) and 40.7% (*n*=238) in SP1 and SP2, respectively. Most of the patients, i.e. 61.4% (*n*=94) and 59.7% (*n*=142) were high-risk compared with standard-risk 37.9% (*n*=58) (*n*=83; 34.9%), while 0.7% (*n*=1) and 5.5% (*n*=13) had missing data for SP1 and SP2, respectively.

For the entire study period, the most common malignancies were leukaemia (*n*=259; 27.7%), brain tumours (*n*=172; 18.4%), lymphoma (*n*=132; 14.1%), nephroblastoma (*n*=75; 8.0%), and soft-tissue sarcomas (*n*=69; 7.4%) (Fig. 1; Supplementary Table 1, https://www.samedical.org/file/2032). Acute leukaemia was the most common type of leukaemia (*n*=184; 71.0%), with ALL subtypes pre-B ALL (*n*=137; 52.9%) and T-ALL (*n*=46; 17.8%), v. acute myeloid leukaemia (AML) (*n*=61; 23.6%). Burkitt lymphoma (BL) was the most common lymphoma (*n*=53; 40.2%), followed by other non-Hodgkin lymphomas (NHL) (*n*=40; 30.3%) and HL (*n*=39; 29.5%). NHL included T-cell lymphomas (*n*=16; 12.1%) and B-cell lymphomas (*n*=3; 2.3%).

Nephroblastoma (*n*=61, 81.3%), neuroblastoma (*n*=40; 83.3%) and retinoblastoma (*n*=29; 96.7%) cases were mostly diagnosed in the 0 - 4 years age group (Supplementary Table 1, https://www.samedical.org/file/2032). Most children with brain tumours were 5 - 9 years of age (*n*=77; 44.8%), while bone tumours were mostly diagnosed in the 10 - 15 years age group (*n*=38; 76%) (Supplementary Table 1, https://www.samedical.org/file/2032). The distribution across the age groups for leukaemia was not notably different: 48.7% (*n*=126), 28.6% (*n*=74) and 22.8% (*n*=59); for the 4 - 5, 5 - 9 and 10 - 15 years age groups, respectively. A similar distribution was observed for soft-tissue sarcoma in 47.8% (*n*=33), 27.5% (*n*=19) and 24.6% (*n*=17) of cases, respectively. Lymphoma was mostly diagnosed in the 5 - 9 (*n*=52; 39.4%) and 10 - 15 years age group (*n*=47; 35.6%), respectively. White children had a notably higher prevalence of leukaemia (*n*=64/156; 41.0%) while black children had the highest prevalence of nephroblastoma (*n*=22/188;

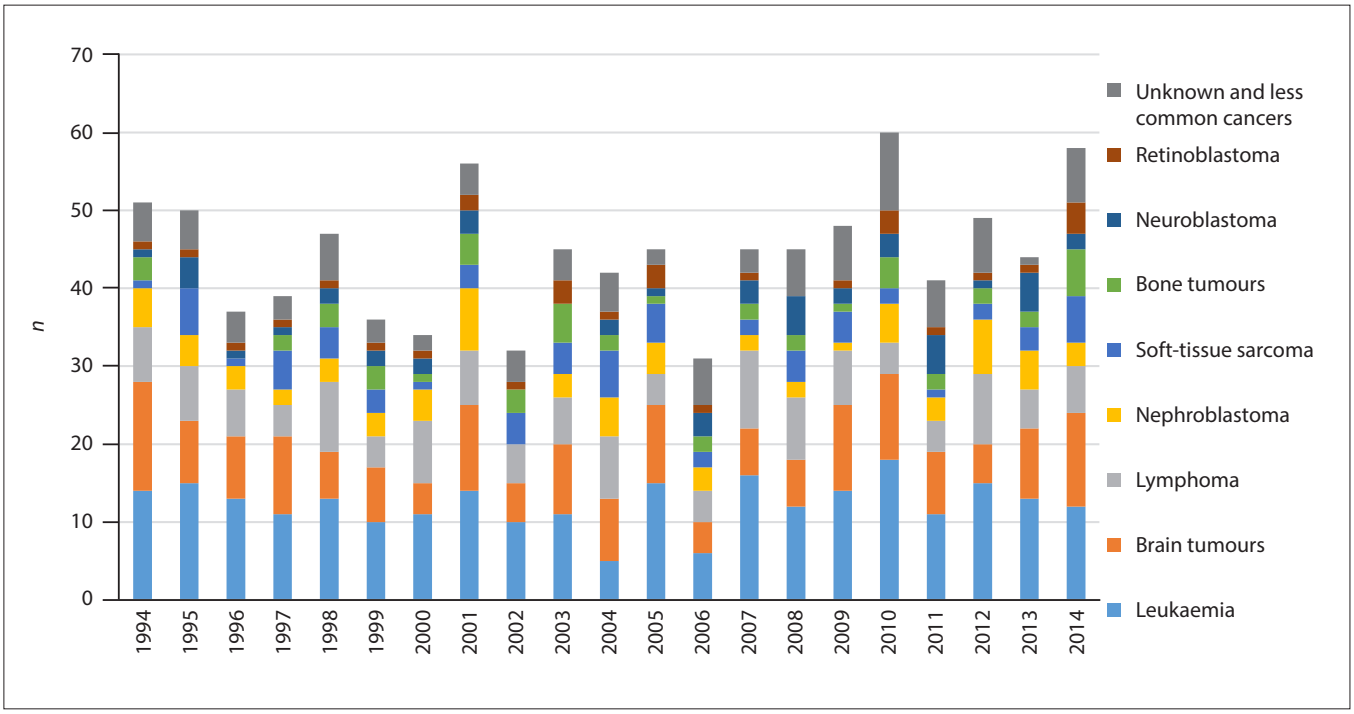

Fig. 1. Distribution of cases by diagnostic group over the years.

Table 1. Distribution of nutritional status at diagnosis during the two study periods (*N*=674)

		Relative frequency %	
Nutritional status	***n***	**SP1 (1994 - 2001) (*n*=266), *n* (%)**	**SP2 (2002 - 2014) (*n*=408), *n* (%)**
Normal	425	163 (61.3)	262 (64.2)
Wasted	66	32 (12)	34 (8.3)
Stunted	61	21 (7.9)	40 (9.8)
Overweight	35	10 (3.8)	25 (6.1)
Severely wasted	28	11 (4.1)	17 (4.2)
Obesity	20	9 (3.4)	11 (2.7)
Severely wasted and stunting	15	8 (3.0)	7 (1.7)
Wasted and stunting	14	7 (2.6	7 (1.7)
Obesity and stunting	6	2 (0.8)	4 (1)
Overweight and stunting	4	3 (1.1)	1 (0.3)

SP = study period.

11.7%), soft tissue sarcoma (*n*=21; 11.2%) and retinoblastoma (*n*=12; 6.4%) compared with other racial groups.

There were no notable differences in the cancer diagnosis distribution between the two study periods, with the mean number of patients per year for SP1 being 44 and 45 for SP2 (Supplementary Table 2, https://www.samedical.org/file/2032). The median (IQR) age in the two study periods was 6 (3 - 10) years and 5 (2 - 9) years, respectively. The proportion of patients in the 0 - 4 years age group increased between the study periods from 42.3% (*n*=148) (SP1) to 49.6% (*n*=290) (SP2), while the proportion of patients in the 5 - 9 years age group decreased slightly from 31.1% (*n*=109) to 29.1% (*n*=170), as well as in the 10 - 15 years age group from 26.6% (*n*=93) to 21.4% (*n*=125). The two study periods had similar male-to-female ratios of 1.3:1.

OS was 60.2% (95% CI 57.0 - 63.4) (Supplementary Table 1, https://www.samedical.org/file/2032) and similar for both study periods, namely 61.1% (95% CI 55.8 - 66.3) for SP1 and 59.7% (95% CI 55.6 - 63.7) for SP2 (p=0.462). Overall, limited- and standard-risk malignancies had a good OS of 81.4% (95% CI 76.7 - 85.5) compared with advanced and high-risk malignancies (48.8%; 95% CI 44.5 - 53.2), with no significant difference between the two study periods (p=0.390 and p=0.740, respectively) (Supplementary Table 2, https://www.samedical.org/file/2032).

Limited disease at diagnosis for solid tumours had an OS of 77.7% (95% CI 70.8 - 83.6) compared with advanced disease (45.6%; 95% CI 39.7 - 51.6; p<0.001) (Fig. 2). For limited disease, there was no significant difference between the two periods, i.e. 75.0% (95% CI 63.0 - 84.7) for SP1 and 79.4% (95% CI 70.5 - 86.6) for SP2 (p=0.654) v. 47.3% (95% CI 37.7 - 57.0) and 44.5% (95% CI 37.0 - 52.2) (p=0.493) for advanced disease, respectively. Underlying cancer (p<0.001), stage at diagnosis (p<0.001), age group (p=0.056), race (p=0.035) and HIV status (p=0.062) were identified as potential risk factors for time to mortality for solid tumours, while study period (p=0.258), sex (p=0.509), comorbid disease (p=0.103) and nutritional status (p=0.345) were not statistically significant. After adjusting for confounders, underlying cancer, stage at diagnosis and race were significantly associated with time to mortality (Supplementary Table 3, https://www.samedical.org/file/2032). Brain tumours (p<0.001), bone tumours (p<0.001), neuroblastoma (p<0.001), soft-tissue sarcoma (p<0.001) and less common solid tumours (p=0.008) worsened OS by 7.1-fold (95% CI 3.4 - 15.0), 9.2-fold (95% CI 4.1 - 20.9), 8.5-fold (95% CI 3.9 - 18.5), 4.9-fold (95% CI 2.2 - 11.0) and 3.0-fold (95% CI 1.3 - 6.6), respectively, compared with nephroblastoma (Supplementary Table 3 (https://www.samedical.org/file/2032)). Advanced solid tumours had an increased risk for death of 2.4 (95% CI 1.6 - 3.4) compared with limited disease (p<0.001) (Supplementary Table 3 (https://www.samedical.org/file/2032)). Nephroblastoma and retinoblastoma had the best OS rates of 89.3% (95% CI 80.1 - 95.3) and 86.7% (95% CI 69.3 - 96.2), respectively (Supplementary Table 1, https://

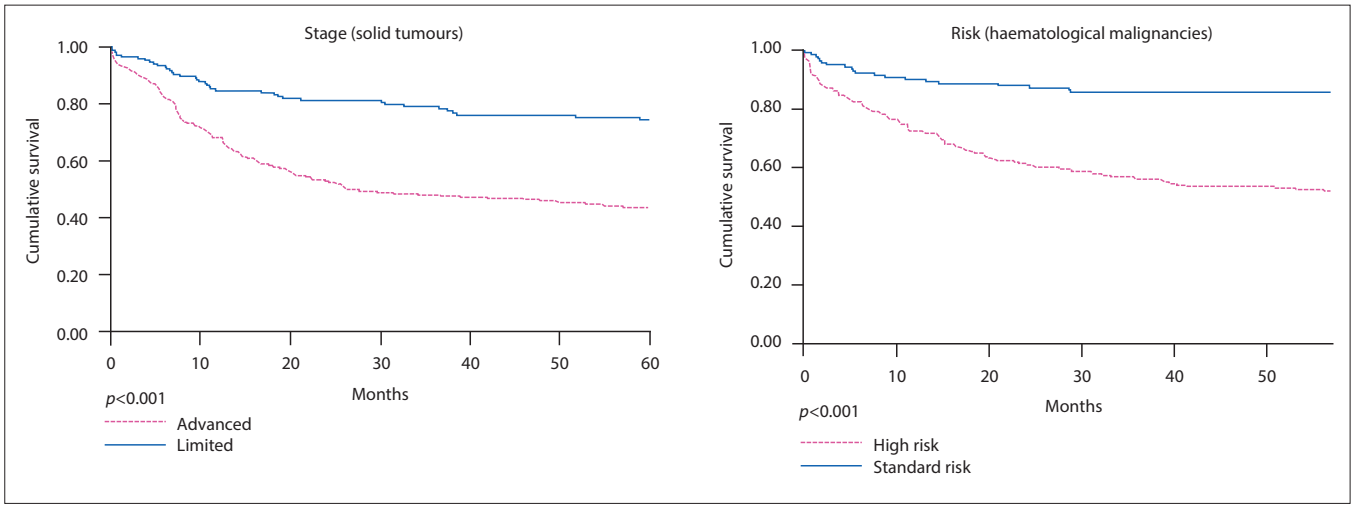

Fig. 2. Kaplan-Meier 5-year survival curves with respect to stage (solid tumours) and risk (haematological malignancies) of disease.

www.samedical.org/file/2032). Both limited and advanced disease nephroblastoma had good OS rates of 92.7% (95% CI 80.1 - 98.5) and 87.1% (95% CI 70.2, 96.4), respectively, while only limited disease for retinoblastoma had a 100% OS rate (95% CI 76.8 - 100.0) v. advanced disease 62.5 (95% CI 24.5 - 91.5). Neuroblastoma had the lowest OS of 27.1% (95% CI 15.3 - 41.8) owing to advanced disease (93.6%). Bone tumours also had an OS of 28.0% (95% CI 16.2 - 42.5), with 51.2% of children diagnosed with advanced disease having the worst OS of only 18.2% (95% CI 5.1 - 40.3), compared with 42.9% (95% CI 21.8 - 66.0) for localised disease. Brain tumours and soft-tissue sarcomas had OS rates of 48.8% (95% CI 41.2 - 56.6) and 52.2% (95% CI 39.8 - 64.4), respectively (Supplementary Table 1, https://www.samedical.org/file/2032).

Black and coloured children had an increased risk for death of 1.8-fold (95% CI: 1.1, 3.1) (p=0.019) and 1.7-fold (95% CI 1.1 - 2.6) (p=0.028), respectfully, compared with white children (Supplementary Table 3, https://www.samedical.org/file/2032). Stage at diagnosis was significantly associated with OS (p<0.001). Of the 70 white children with solid tumours, 26 (37.1%) presented with limited disease, 36 (51.4%) had advanced disease and 8 (11.4%) had missing data, while 36 (29.5%) of the 122 black children had limited disease, 58 (47.5%) had advanced disease, and 28 (23.0%) had missing data. Of the 351 coloured children, 112 (31.9%) had limited disease, 189 (53.9%) had advanced disease and 50 (14.3%) had missing data. Nutritional status at diagnosis was noted in 119 (76.3%) white, 117 (62.2%) black and 435 (74.0%) coloured children. Although nutritional status was not statistically significant (p=0.345), more white children (n=86; 72.3%) had a normal nutritional status compared with black (n=77; 65.8%) and coloured (n=260; 59.8%) children. There were no significant differences in OS for solid tumours between the two study periods (p=0.257). The OS for advanced-risk brain tumours improved, albeit non-significantly, from 34.3% (95% CI 19.1 - 52.2) in SP1 to 45.8% (95% CI 31.4 - 60.8) in SP2 (p=0.354) and advanced nephroblastoma from 82.4% (95% CI 55.6 - 96.2) to 92.9% (95% CI 66.1 - 99.8), respectively (p=0.434) (Supplementary Table 2, https://www.samedical.org/file/2032).

Haematological malignancies had an OS of 65.0% (95% CI 60.0 - 69.7), while standard-risk leukaemia and lymphoma patients had OS rates of 85.9% (95% CI 79.1 - 91.2) compared with high-risk disease, which had an OS rate of 52.8% (95% CI 46.2 - 59.3) (p<0.001) (Fig. 2). There was no significant difference in OS for both standard-risk and high-risk haematological malignancies between the two study periods, i.e. 83.1% (95% CI 71.0 - 91.6) in SP1 and 88.0% (95% CI 79.0 - 94.1) in SP2 (p=0.404) for the standard-risk group and 51.6% (95% CI 41.0 - 62.1) and 53.5% (95% CI 45.0 - 61.9)) (p=0.772) for the high-risk group, respectively. For haematological malignancies, the subtype (p=0.002), risk group (p<0.001), and comorbid disease (p=0.009) were identified as potential risk factors for mortality, while there was no difference in time to mortality for nutritional status (p=0.874), study period (0.769), HIV status (p=0.582), sex (p=0.443), age group (p=0.411) and race (p=0.203). The subtype (p<0.001) and risk group (p<0.001) were significantly associated with mortality after adjusting for confounders (Supplementary Table 4, https://www.samedical.org/file/2032). Children diagnosed with high-risk disease had a 4.2-fold higher risk of death (95% CI 2.6 - 6.8) compared with children diagnosed with standard-risk disease (p<0.001) (Supplementary Table 4, https://www.samedical.org/file/2032). Being diagnosed with leukaemia increased the chances of death 2.3-fold (95% CI 1.5 - 3.6) compared with being diagnosed with lymphoma (p<0.001) (Supplementary Table 4 (https://www.samedical.org/file/2032)). Lymphoma had a superior OS of 76.5% (95% CI 68.4 - 83.5) compared with that of leukaemia (59.1%; 95% CI 52.8 - 65.1) (Supplementary Table 1, https://www.samedical.org/file/2032). ALL had the best OS, i.e. 69.6% (95% CI 62.4 - 76.1), while AML had a poor OS rate of 29.5% (95% CI 18.5 - 42.6; p<0.001), with no significant difference between the two study periods (p=0.822 and p=0.855, respectively). Standard-risk BL (Supplementary Table 2, https://www.samedical.org/file/2032) and HL (Supplementary Table 1, https://www.samedical.org/file/2032) had excellent OS rates of 100.0% (95% CI 69.2 - 100.0) and 89.2% (95% CI 75.8 - 97.1) respectively. High-risk HL improved non-significantly from 66.7% (95% CI 9.4 - 99.2) during SP1 to 86.7% (95% CI 59.5 - 99.3) during SP2 (p=0.364) (Supplementary Table 2, https://www.samedical.org/file/2032). T-ALL had a lower OS rate of 56.5% (95% CI 41.1 - 71.1) compared with 74.5% for pre-B ALL (95% CI: 66.3, 81.5) (Supplementary Table 1, https://www.samedical.org/file/2032), with no significant difference between the two study periods (p=0.837 for pre-B ALL and p=0.422 for T-ALL). There were non-statistically significant improved OS rates for high-risk pre-B ALL from 37.5% (95% CI 15.2 - 64.6) in SP1 to 48.6% (95% CI 31.9 - 65.6) in SP2 (p=0.493) and T-ALL from 46.7% (95% CI 21.3 - 73.4) to 61.3% (95% CI 42.2 - 73.8), respectively (p=0.422) (Supplementary Table 2, https://www.samedical.org/file/2032).

There were 674 (72.1%) patients with nutritional data at diagnosis available for sub-analysis, of whom the majority had a normal nutritional status: 61.3% (n=163) and 64.2% (n=262) for the two

study periods, respectively. During SP1, 12.0% (*n*=32) were wasted and 4.1% (*n*=11) were severely wasted – these values were similar in SP2, i.e. 8.3% (*n*=34) and 4.2% (*n*=17), respectively (Table 1). SP1 had 3.8% (*n*=10) overweight children and 3.4% (*n*=9) obese children, while 6.1% (*n*=25) were overweight and 2.7% (*n*=11) were obese in SP2. A minority of children were stunted, i.e. 7.9% (*n*=21) and 9.8% (*n*=40) in the two study periods, respectively (Table 1). A small number of patients (*n*=41; 4.4%) had a comorbidity at diagnosis, which included 26 (2.8%) patients with HIV/AIDS, 8 (0.9%) with tuberculosis (TB), 5 (0.5%) with trisomy 21, and two (0.2%) with tuberous sclerosis. After adjusting for all other factors, trisomy 21 was the only comorbid disease that showed a trend towards significance in haematological malignancies, with an increased risk for death of 2.4 (95% CI 0.9 - 6.7; *p*=0.082) (Supplementary Table 4, https://www.samedical.org/file/2032). Most patients with trisomy 21 had AML (*n*=4; 80.0%) and one had pre-B ALL.

Discussion

Hesseling *et al.*[13] previously published the disease profiles and outcomes of children treated at Tygerberg Hospital between 1983 and 1993 and identified the five most common childhood cancers as leukaemia, lymphoma, brain tumours, nephroblastoma and neuroblastoma. In our follow-up study at Tygerberg Hospital, there was an increase in soft-tissue sarcomas, replacing neuroblastoma in the top five diagnoses. Leukaemia was still the most common childhood cancer, which was consistent with a 2021 report by Johnston *et al.*[3] on regional and global incidence of childhood cancer. Lymphoma was reported to be more prevalent in Western Africa,[18,19] while in this study it was the third most prevalent childhood cancer. Liu *et al.*[20] reported that boys had an estimated 5 - 48% higher chance of being diagnosed with childhood cancers. This finding was confirmed in the present study, with a male to female ratio of 1.3:1, which was also similar to the ratio reported in Northwest Cameroon (1.4:1).[19] The notable sex difference for lymphoma and T-ALL with an increased prevalence for males, reported by Steliarova-Foucher *et al.*[2] and Dores *et al.*,[21] respectively, was consistent with the findings of the present study.

Coloured children (elsewhere referred to as mixed race)[17] comprised the majority of the patients, followed by black and white children, which reflected the demography of the Western Cape, SA.[17] The increase in the number of black children and decrease in the number of white children during the second time period (2002 - 2014) could most likely be attributed to the population shift that happened after the political change to a democracy in 1994, as black South Africans were free to migrate to urban areas throughout the country.[22] Black children had a high nephroblastoma prevalence, which was consistent with other epidemiological studies in Africa.[23] White children were reported to have a high leukaemia incidence, which was consistent with the findings of the present study.[24,25]

Spector *et al.*[8] reported a peak in childhood cancer incidence between the ages of 2 and 5 years, which was similar to the findings in the present study, where the majority of the patients were between 0 and 4 years of age. Brain tumours were more common in the 5 - 9 years age group, which was similar to reports in the UK.[26] Most bone tumour cases were diagnosed in the 10- to 15-year age group, as expected, owing to the association with the adolescent growth spurt.[8]

Survival rates in LMICs are reported to be significantly lower compared with HICs.[2] In the present study, patients with limited disease, standard-risk and haematological malignancies had a good OS rate of 81.4%, similar to survival rates reported in HICs, where the OS was estimated to be between 78% and 83% for all cancers combined.[7] In LMICs there are several barriers to successful treatment such as late diagnosis in advanced disease, limited access to healthcare, inadequate education on childhood cancer, treatment refusal or absconding treatment, poor referral efficiency or other unknown reasons that contribute to a lower OS.[25,27] Some of these factors might have been the reason for the low OS of 60.2% in the present study, as 61.8% of the solid-tumour patients had advanced disease while 60.1% of the haematological malignancy patients were high-risk, probably owing to late diagnosis. The racial disparities could be attributed to socioeconomic factors or underutilisation of healthcare services.[25,28] White children presented earlier, had better OS rates and were more likely to have normal nutritional status at diagnosis compared with black and coloured children. OS for nephroblastoma was reported to be ≥90% in HICs, which was similar to the OS for nephroblastoma in the present study, i.e. 89.3%.[29] The majority of nephroblastoma tumours likely had favourable histology, as both limited and advanced disease had excellent OS rates. OS for retinoblastoma improved, compared with a previous study[13] done at Tygerberg Hospital during a 10-year period from 1983 to 1993, from 52% to 86.7% in 1994 - 2014; however, this value was not comparable with the excellent OS reported in HICs of nearly 100%, although limited disease had a 100% OS in the present study.[13,31]

The OS (29.5%) for AML improved compared with a previous study[13] where it was only 15%, albeit not near the OS in Europe, i.e. ~66.8%.[7] T-ALL is associated with poor OS confirmed in this study.[31] There were also improved treatment outcomes for lymphoma as compared with the previously mentioned study by Hesseling *et al.*[13] There was a notable improvement for standard-risk BL from 60% in 1983 - 1993 to 100% for the 1994 - 2014 study period, probably due to the use of LMB-based protocols.[13,16] Even high-risk BL improved from 15% in 1983 - 1993[13] to 71.8% in 1994 - 2001 and 70% in 2002 - 2014. Two hospitals in Northwest Cameroon estimated their OS for BL at 52% for the years 2008 - 2014.[32]

Poor nutritional status at diagnosis was not negatively associated with OS. This is probably due to the limited number of children who presented with either stunting or moderate-to-severe malnutrition in our study population. This could also be the result of the nutritional interventions provided by the POU, as nutrition is actively managed on an in- and outpatient basis. In a Brazilian study,[33] OS was not affected by malnutrition at diagnosis. Comorbidities such as HIV are a burden in LMICs, as they are associated with certain childhood cancers and have been reported to increase mortality rates in children with cancer.[9,10] In the present study there was a trend towards significance for the association with comorbid diseases, but a larger sample size would be needed to confirm the association. The study periods analysed here span a period when ART was not the standard of care in SA and there was a lot of stigma surrounding HIV.[34] The HIV status of most patients was unknown in the first period, while it was known for most patients in the second period and supportive care could be offered.

During the first study period there was less emphasis on the early warning signs of childhood cancer in SA, as the local Saint Siluan early warning signs of childhood cancer guideline was only developed in 1999 and adopted in 2000.[35] A higher percentage of patients in the second period had a missing stage at diagnosis and therefore it was difficult to determine the impact of this document. Continued and intensified education of the community and healthcare workers regarding the warning signs of childhood cancer is crucial to improve early recognition of childhood cancer.[14] There was no significant difference in cancer diagnosis trends and OS between the two study periods, which could mean that the epidemiology of childhood cancer remained similar and there was good adherence to standard treatment protocols over the course of the two study periods.

Study limitations

The retrospective analysis of a single institution's patient population was not representative of the larger SA population.

Conclusion

Limited solid-tumour burden and standard-risk haematological malignancies had similar OS rates to that reported in HICs, with major improvements in OS for nephroblastoma, retinoblastoma and BL compared with a similar study conducted in 1995.[13] There is a crucial need to link the local national childhood cancer registry to clinical and pathology-based registries to improve data capturing and further investigate ways of improving early diagnosis. Education programmes should be implemented and, importantly, evaluated for their impact.

Declaration. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements. The African Cancer Institute (ACI) for support in funding SN's MPhil (Cancer Science) degree, the South African Children Study Group and MK for providing access to the tumour registries.

Author contributions. MK conceptualised and developed the initial protocol and presented preliminary data at the SIOP 2015 meeting in Dublin. SN collected and analysed the data, with supervision from MK and TME. TME performed the statistical analysis and SN wrote the manuscript. MK and TME assisted with data analysis and critically revised and edited the manuscript. RU and AVZ assisted with data collection, critical revision and editing of the manuscript. All authors read and approved the manuscript.

Funding. None.

Conflicts of interest. None.

1. National Center for Health Statistics. LCWK1. Deaths, Percent of Total Deaths, and Death Rates for the 15 Leading Causes of Death in 5-Year Age Groups, by Race and Sex: United States, 1999 - 2015. Atlanta: Centers for Disease Control and Prevention, 2017. https://www.cdc.gov/nchs/nvss/mortality/lcwk1.htm (accessed 19 June 2023).
2. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001 - 10: A population-based registry study. Lancet Oncol 2017;18(6):719-731. https://doi.org/10.1016/S1470-2045(17)30186-9
3. Johnston WT, Erdmann F, Newton R, Steliarova-Foucher E, Schüz J, Roman E. Childhood cancer: Estimating regional and global incidence. Cancer Epidemiol 2021;71(PB):101662. https://doi.org/10.1016/j.canep.2019.101662
4. Stefan DC, Stones DK. The South African Paediatric Tumour Registry – 25 years of activity. S Afr Med J 2012;102(7):605-606. https://doi.org/10.7196/samj.5719
5. Steliarova-Foucher E, Fidler MM, Colombet M, et al. Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991 - 2010 (Automated Childhood Cancer Information System): A population-based study. Lancet Oncol 2018;19(9):1159-1169. https://doi.org/10.1016/S1470-2045(18)30423-6
6. Stones DK, De Bruin GP, Esterhuizen TM, Stefan DC. Childhood cancer survival rates in two South African units. S Afr Med J 2014;104(7):501-504. https://doi.org/10.7196/samj.7882
7. 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(1):35-47. https://doi.org/10.1016/S1470-2045(13)70548-5
8. Spector LG, Pankratz N, Marcotte EL, Fellow P. Genetic and nongenetic risk factors for childhood cancer. Pediatr Clin North Am 2015;62(1):11-25. https://doi.org/10.1016/j.pcl.2014.09.013
9. Stiller CA. Epidemiology and genetics of childhood cancer. Oncogene 2004;23(38):6429-6444. https://doi.org/10.1038/sj.onc.1207717
10. Davidson A, Wainwright RD, Stones DK, et al. Malignancies in South African children with HIV. J Pediatr Hematol Oncol 2014;36(2):111-117. https://doi.org/10.1097/MPH.0b013e31829cdd49
11. World Health Organization. Improving childhood cancer cure rate. Geneva: WHO, 2023. https://www.who.int/activities/improving-childhood-cancer-cure-rate (accessed 24 June 2021).
12. Pui C, Pei D, Pappo AS, et al. Treatment outcomes in black and white children with cancer: Results from the SEER Database and St Jude Children's Research Hospital, 1992 through 2007. J Clin Oncol 2012;30(16):2005-2012. https://doi.org/10.1200/JCO.2011.40.8617
13. Hesseling PB, Wessels G, van Riet FA. The Tygerberg Hospital Children's Tumour Registry 1983 - 1993. Eur J Cancer 1995;31(9):1471-1475. https://doi.org/10.1016/0959-8049(95)00289-U
14. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica 2020;105(11):2524-2539. https://doi.org/10.3324/haematol.2020.247031
15. Elgarten CW, Aplenc R. Pediatric acute myeloid leukemia: Updates on biology, risk stratification, and therapy. Curr Opin Pediatr 2020;32(1):57-66. https://doi.org/10.1097/MOP.0000000000000855
16. Moleti ML, Al-Jadiry MF, Shateh WA, et al. Long-term results with the adapted LMB 96 protocol in children with B-cell non-Hodgkin lymphoma treated in Iraq: Comparison in two subsequent cohorts of patients. Leuk Lymphoma 2019;60(5):1224-1233. https://doi.org/10.1080/10428194.2018.1519810
17. Statistics South Africa. Provincial Profile: Western Cape Census 2011. Pretoria: StatsSA, 2014.
18. Cristina Stefan D. Patterns of distribution of childhood cancer in Africa. J Trop Pediatr 2015;61(3):165-173. https://doi.org/10.1093/tropej/fmv005
19. Afungchwi GM, Kruger M, Wharin PD, Bardin R, Kouya FN, Hesseling PB. The evolution of a hospital-based cancer registry in Northwest Cameroon from 2004 to 2015. J Trop Pediatr 2020;67 (3):5-14. https://doi.org/10.1093/tropej/fmaa038
20. Liu Z, Yang Q, Cai N, Jin L, Zhang T, Chen X. Enigmatic differences by sex in cancer incidence: Evidence from childhood cancers. Am J Epidemiol 2019;188(6):1130-1135. https://doi.org/10.1093/aje/kwz058
21. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001 - 2007. Blood 2012;119(1):34-43. https://doi.org/10.1182/blood-2011-04-347872
22. Bakker JD, Parsons C, Rauch F. Migration and urbanization in post-apartheid South Africa. The World Bank Econ Rev 2020;34(2):509-532. https://doi.org/10.1093/wber/lhy030
23. Stiller CA, Parkin2 DM. International variations in the incidence of childhood renal tumours. Br J Cancer 1990;62(6):1026-1030. https://doi.org/10.1038/bjc.1990.432
24. Hesseling PB, Hartley P, Zietsman L, van Lill S, Preston-Martin S, Wessels G. Incidence of acute lymphoblastic leukaemia in white and coloured children in the Western Cape. S Afr Med J 2004;94:(7):533-536. https://doi.org/10.7196/SAMJ.2640
25. Erdmann F, Kielkowski D, Schonfeld SJ, et al. Childhood cancer incidence patterns by race, sex and age for 2000 - 2006: A report from the South African National Cancer Registry. Int J Cancer 2015;136(11):2628-2639. https://doi.org/10.1002/ijc.29308
26. Stiller CA, Bayne AM, Chakrabarty A, Kenny T, Chumas P. Incidence of childhood CNS tumours in Britain and variation in rates by definition of malignant behaviour: Population-based study. BMC Cancer 2019;19(1):139. https://doi.org/10.1186/s12885-019-5344-7
27. Kruger M, Hendricks M, Davidson A, et al. Childhood cancer in Africa. Pediatr Blood Cancer 2014;61(4):587-592. https://doi.org/10.1002/PBC.24845
28. Pui C-H, Pei D, Pappo AS, et al. Treatment outcomes in black and white children with cancer: Results from the SEER Database and St Jude Children's Research Hospital, 1992 through 2007. J Clin Oncol 2012;30(16):2005-2012. https://doi.org/10.1200/JCO.2011.40.8617
29. Van Den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, et al. Position Paper: Rationale for the treatment of Wilms' tumour in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol 2017;14(12):743-752. https://doi.org/10.1038/nrurol.2017.163
30. Fabian ID, Abdallah E, Abdullahi SU, et al. Global retinoblastoma presentation and analysis by national income level. JAMA Oncol 2020;6(5):685-695. https://doi.org/10.1001/jamaoncol.2019.6716
31. Van Grotel M, Van Den Heuvel-Eibrink MM, Van Wering ER, et al. CD34 expression is associated with poor survival in pediatric T-cell acute lymphoblastic leukemia. Pediatr Blood Cancer 2008;51(6):737-740. https://doi.org/10.1002/pbc.21707
32. Afungchwi GM, Hesseling P, van Elsland SL, Kouya F, Kruger M. Destitution, treatment adherence and survival of children with Burkitt lymphoma in a twinning programme in Northwest Cameroon. Pediatr Blood Cancer 2019;66(12):1-8. https://doi.org/10.1002/pbc.27946
33. Viani K, Barr RD, Filho VO, Ladas EJ. Nutritional status at diagnosis among children with cancer referred to a nutritional service in Brazil. Hematol Transfus Cell Ther 2021;43(4):389-395. https://doi.org/10.1016/J.HTCT.2020.04.008
34. Nyblade L, Stangl A, Weiss E, Ashburn K. Combating HIV stigma in health care settings: What works? J Int AIDS Soc 2009;12(1):15. https://doi.org/10.1186/1758-2652-12-15
35. Stones DK. Childhood cancer: Early warning signs. Continuing Med Ed 2010;28(7):314.

Accepted 10 February 2022.