# Paediatric nephroblastoma at a South African tertiary hospital: A 21-year retrospective analysis

**E Brits,**[1] MB ChB, MMed (Surg); **E Gerber,**[1] medical student; **I Iroka,**[1] medical student; **L Mgidlana,**[1] medical student; **J Willoughby,**[1] medical student; **S Dhlamini,**[1] medical student; **P Nxumalo,**[1] medical student; **S Sefadi,**[1] medical student; **A Mthembu**,[1] medical student; **J B Sempa,**[2] PhD

[1] *Department of Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa*
[2] *Department of Biostatistics, School of Biomedical Sciences, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa*

***Corresponding author:*** *E Brits (lizettebrits@gmail.com)*

**Background.** Nephroblastoma (Wilms tumour) is one of the most common solid tumours of all paediatric cancers (prevalence of 5% globally and 13.5% in South Africa (SA)), with suboptimal survival outcomes, impacting children's lives. Consequently, there is an urgent need for enhanced early detection strategies, addressing survival rate disparities and late-stage presentations to improve outcomes.
**Objectives.** To assess profiles, disease presentations, management and outcomes of patients with nephroblastoma at Universitas Academic Hospital Complex (UAHC), and to compare patients from SA and Lesotho, including differences between early and late presenters and reasons for delayed presentation.
**Methods.** This retrospective cross-sectional study included 207 paediatric oncology patients treated for nephroblastoma at the Paediatric Haematology and Oncology Unit at UAHC, Bloemfontein, SA, from January 2000 to December 2020.
**Results.** The median age of the study population was 38 months, with a marginal male predominance (50.7%). A 1-month delay occurred between symptom onset and diagnosis, commonly attributed to delayed care-seeking, impacting survival rates. Compared with similar SA studies, a higher stage IV disease rate (29.5%) was observed, and encouraging survival rates (59.4%) correlated with favourable preoperative histology and no relapse. In comparison, Lesotho patients experienced longer delays and presented with more severe disease.
**Conclusion.** This study highlights the need for collaboration between SA and Lesotho healthcare providers to improve outcomes by addressing diagnostic delays, treatment defaults and response variations in resource-limited settings through community health education, improving access to primary care, offering care-provider training, improving diagnostic resources and addressing socioeconomic barriers.

**Keywords:** nephroblastoma, Wilms tumour, paediatric oncology, diagnostic delays, treatment outcomes, resource-limited settings

*S Afr Med J* 2024;114(12):e2223. https://doi.org/10.7196/SAMJ.2024.v114i12.2223

Nephroblastoma (Wilms tumour) is a childhood malignancy primarily affecting the kidneys.[1] It accounts for ~5% of all paediatric cancers globally, and is the most common form of renal cancer in children aged <15 years,[2] significantly impacting young lives.[3] Its prevalence in South Africa (SA) (10% - 13.5%) is concerning,[4-6] presenting a considerable healthcare challenge that demands immediate attention and thorough investigation.[2,4-8]

The clinical manifestation typically includes the insidious development of an asymptomatic abdominal mass, abdominal discomfort, haematuria, hypertension and urinary tract infections.[1,9] The disease can affect a single kidney or both kidneys. Diagnosis relies on meticulous physical examinations, urinalysis and comprehensive imaging studies.[1,9] Consequently, asymptomatic patients may not be identified until the disease is advanced.

Early detection and appropriate treatment are crucial for managing nephroblastoma.[4,10] The standard of care in SA aligns with a modified International Society of Paediatric Oncology (SIOP) protocol for African countries.[9] It classifies the disease into five distinctive stages based on parameters such as tumour extent, histological characteristics and bilateral involvement, guiding treatment strategies and predicting patient outcomes.[9] There is variation across stages, with slightly more cases of stages I (30 - 37%) and III (24 - 32%) compared with stage II (18%) and stage IV (21%) in SA studies.[7,8] These discrepancies could stem from treatment protocol differences, such as the National Wilms Tumour Study Group protocol at the Red Cross Children's Hospital in Cape Town, SA,[8] or from demographic variations.[4,5,7,8,10]

Global survival rates for nephroblastoma exhibit significant disparities, with developed nations reporting 4-year rates of up to 90%.[2,4] This starkly contrasts with sub-Saharan African figures, ranging from 11% in Sudan to 66% in SA.[10,11] These variations result from multifaceted factors, including late-stage disease presentation in lower-income countries, compromised health indicators and treatment abandonment due to socioeconomic challenges.[9,11,12] Recognising these intricacies becomes pivotal for tailoring interventions and improving outcomes.

Late presentation in developing countries poses a significant challenge, negatively impacting treatment outcomes and overall survival.[9,11,13] A retrospective study at the Universitas Academic Hospital Complex (UAHC) in Bloemfontein and Tygerberg Hospital in Stellenbosch, SA, located in the Free State and Western Cape provinces, respectively, underscored the correlation between disease staging and survival rates, reporting 81%, 69%, 58% and 46% for stages I to IV, respectively.[4] Black African children presenting at later stages experienced diminished survival rates, potentially linked to delayed presentation, poor nutritional status and comorbidities such as HIV and tuberculosis.[4,10]

Timely and appropriate medical care is critical to prevent delayed diagnoses resulting in advanced disease stages. Contributing factors to delayed presentation include limited access to primary care

and diagnostic resources, poverty and the pursuit of unorthodox treatments.[13-17] Compounding the issue are parental negligence, delays in referral and treatment default.[17-19]

The UAHC in central SA encounters unique challenges stemming from limited healthcare resources, late-stage disease presentations and socioeconomic disparities.[20-23] Understanding the patient profile, disease presentation, treatment modalities and outcomes at this facility is essential. Furthermore, addressing the factors underlying delayed referrals for treatment could improve survival rates.[4,10,24] Examining cultural and regional influences on healthcare-seeking behaviour and treatment accessibility may reveal challenges faced by healthcare providers and patients.

This study investigated nephroblastoma among paediatric patients at the UAHC to determine challenges affecting patient outcomes. The high prevalence of nephroblastoma in SA[4-6] emphasises the need for targeted research and healthcare efforts, as well as early detection mechanisms to improve survival rates and reduce disparities among diverse demographic groups. The aim of the study was to describe the profile of patients treated for nephroblastoma at UAHC, including their disease presentation, management and outcomes, and furthermore, to compare patients who survived v. died, and SA v. Lesotho patients, and gain insights into the reasons for delayed presentations.

# Methods

## Study context

The Free State Province, SA, provides paediatric oncology services to most of central SA, including parts of the Eastern and Northern Cape provinces and the neighbouring Lesotho.

## Study participants and measurement

This retrospective cross-sectional study encompassed all paediatric oncology patients who underwent treatment for nephroblastoma at the Paediatric Haematology and Oncology Unit at UAHC, Bloemfontein, from January 2000 to December 2020. Data for this study were sourced from the Paediatric Haematology and Oncology Tumour Registry and individual patient records. Data collected included demographic, diagnostic, treatment and outcome information.

## Pilot study

A pilot study was undertaken with the initial 10 patients to assess the data collection feasibility and the datasheet's adequacy. Subsequently, no modifications were made to the data collection form, and these patients were incorporated into the main study.

## Data analysis

Data were captured on a Microsoft 365 Excel spreadsheet (version 2307; Microsoft Corporation, USA) and analysed by the Department of Biostatistics, Faculty of Health Sciences, University of the Free State. We performed the statistical analysis using R (version 4.3.0; R Foundation for Statistical Computing, Austria). Results were summarised by frequencies and percentages (categorical variables) and mean and standard deviations (numerical variables). Subgroups were compared using $\chi^2$ or Fisher's exact tests (categorical variables) and Mann-Whitney or Kruskal-Wallis tests (numerical variables). The 95% confidence intervals (CIs) were calculated for differences between medians of subgroups.

For univariate analysis, an adjusted Cox proportional hazard model was used, adjusting for specific variables associated with the survival of patients with nephroblastoma, such as high-risk stratification, metastasis to the lungs, metastasis to more than one site, histology (anaplastic and blastemal type nephroblastoma), age at diagnosis and chemotherapy. Multivariate analysis determined the factors affecting the survival of paediatric nephroblastoma, using a standard Cox proportional hazards model for time to mortality. We adjusted for all factors from the univariate analysis. We summarised the results with an adjusted hazard ratio (adj. HR), 95% CI and *p*-value, and constructed an adjusted Kaplan-Meier curve for risk stratification.

## Ethical considerations

Ethics approval was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (ref. no. UFS-HSD2021/0448/3108) and the Free State Province Department of Health. Patient information was anonymised, and no identifying details were documented. Data were stored on a password-protected computer to ensure data security. Because data were collected from archived patient records, informed consent was not required.

# Results

## Demographic variables

In total, 207 patients' files were included in the study, of whom 50.7% (*n*=105) were male. The majority were black (*n*=176; 85.0%) (Table 1). The median (interquartile range (IQR)) diagnosis age was 38 (24 - 63) months (Table 2), with 59.4% (*n*=123) diagnosed <4 years of age. Geographically, the majority of patients were from SA (*n*=151; 72.9%) (Table 1), mainly from the Free State Province (*n*=111; 73.5%), followed by the Northern Cape (*n*=31; 20.5%), North West (*n*=4; 2.6%), Eastern Cape (*n*=4; 2.4%) and one (0.5%) patient from Mpumalanga.

## Diagnostic aspects

The median (IQR) symptom-to-diagnosis time was 30 (10 - 60) days (Table 2), ranging from immediate to 1 year. Notably, 56.0% of patients (*n*=116/207) experienced symptoms for >2 weeks before presenting at UAHC. In 47.4% (*n*=55) of these cases, no specific reasons were provided for the delay in diagnosis (Table 1). Stage I disease was diagnosed in 80 (38.6%), patients followed by stage IV (*n*=61; 29.5%). Some patients died before definitive staging or treatment, comprising an unstaged group of 4.3% (*n*=9, including one with metastasis). No significant correlation between tumour stage and the duration of symptoms was found (*p*>0.9) (Table 1).

Tumours were primarily unilateral (*n*=195; 94.2%), with a slight left-sided kidney tumour predominance in 51.3% (*n*=100/195) of these patients (Table 1). At diagnosis, the median (IQR) lactate dehydrogenase (LDH) level, indicating tissue injury and tumour burden, was 783 (137 - 494) U/L (Table 2). Metastatic disease was found at diagnosis in 32.4% (*n*=67) of patients, with the lungs being the most prevalent site (*n*=46/67; 66.7%) (Table 1). Negative isotope studies demonstrated skeletal involvement in 143 (69.1%) patients, liver involvement in 128 (61.8%) and clear bone marrow aspirates in 189 (91.3%).

Based on risk stratification, patients were predominantly categorised as being in the intermediate risk category (*n*=121; 58.5%). Low-risk cases constituted only 1.4% (*n*=3), while in 5.3% (*n*=11), risk stratification was not determined (Table 1). Tumour histology revealed intermediate risk in 159 (76.8%) patients, high risk in 12 (8.8%) and low risk in 8 (3.9%) patients. Table 3 summarises the breakdown of specific histology findings per risk group. In all 8 low-risk patients, histological investigations showed necrosis.

## Treatment

In 98.1% (*n*=203) of cases, patients adhered to the modified SIOP protocol for African nations,[9] while 1.9% (*n*=4/207) did not. As

**Table 1. Comparison between patients who were alive and died by the end of the study period (*N*=207)**

| Variable | Total, *n* (%) | Alive (*n*=123), *n* (%) | Died (*n*=84), *n* (%) | *p*-value* |
|---|---|---|---|---|
| Sex | | | | 0.3 |
| Male | 105 (50.7) | 59 (48.0) | 46 (54.8) | |
| Female | 102 (49.3) | 64 (52.0) | 38 (45.2) | |
| Ethnicity | | | | 0.5 |
| Black | 176 (85.0) | 105 (85.4) | 71 (84.5) | |
| White | 11 (5.3) | 8 (6.5) | 3 (3.6) | |
| Mixed race | 20 (9.7) | 10 (8.1) | 10 (11.9) | |
| Country | | | | 0.7 |
| Lesotho | 56 (27.1) | 32 (26.0) | 24 (28.6) | |
| South Africa | 151 (72.9) | 91 (74.0) | 60 (71.4)) | |
| Diagnosis | | | | |
| Delayed >2 weeks | 116 (56.0) | 70 (56.9) | 46 (55.4) | <0.001 |
| No reason | 55 (47.4) | 30 (42.9) | 25 (54.3) | 0.2 |
| Delayed seeking care | 21 (18.1) | 14 (20.0) | 7 (15.2) | 0.5 |
| Delayed referral | 26 (22.4) | 19 (27.1) | 7 (15.2) | 0.13 |
| Wrong initial diagnosis | 11 (9.5) | 5 (7.1) | 6 (13.0) | 0.3 |
| Passport problems | 2 (1.7) | 2 (2.9) | 0 (0) | 0.5 |
| Other | 1 (0.9) | 0 (0) | 1 (2.2) | 0.4 |
| Tumour side | | | | 0.052 |
| Unilateral | 195 (94.2) | 117 (95.1) | 78 (92.9) | |
| Left | 100 (51.3) | 68 (55.3) | 32 (38.1) | |
| Right | 95 (48.7) | 49 (39.8) | 46 (54.8) | |
| Bilateral | 12 (5.8) | 6 (4.9) | 6 (7.1) | |
| Metastasis | 67 (32.4) | 26 (21.1) | 41 (48.8) | <0.001 |
| Site of metastasis (*n*=67) | | | | |
| Lungs | 46 (68.9) | 21 (17.1) | 25 (29.8) | 0.031 |
| Liver | 21 (31.3) | 7 (5.7) | 14 (16.7) | 0.010 |
| Inferior vena cava | 6 (9.0) | 0 (0) | 6 (7.1) | 0.004 |
| Bone marrow | 4 (6.0) | 1 (0.8) | 3 (3.6) | 0.3 |
| Stage | | | | |
| I | 80 (38.6) | 67 (54.5) | 13 (15.5) | <0.001 |
| II | 24 (11.6) | 17 (13.8) | 7 (8.3) | 0.2 |
| III | 22 (10.6) | 9 (7.3) | 13 (15.3) | 0.061 |
| IV | 61 (29.5) | 25 (20.3) | 36 (42.9) | <0.001 |
| V | 11 (5.3) | 5 (4.1) | 6 (7.1) | 0.4 |
| Unstaged | 9 (4.3%) | 0 (0) | 9 (4.3%) | |
| Treatment | | | | |
| Received neo-adjuvant chemotherapy | 196 (94.7) | 121 (98.4) | 75 (89.3) | 0.008 |
| Response to chemotherapy (*n*=196) | | | | 0.002 |
| Good | 135 (68.9) | 92 (74.8) | 43 (51.2) | |
| Poor | 40 (20.4) | 22 (17.9) | 18 (21.4) | |
| Unknown | 21 (10.7) | 7 (5.7) | 14 (16.7) | |
| Received surgery | 180 (87.0) | 123 (100) | 57 (67.9) | |
| Received radiotherapy | 37 (17.9) | 17 (13.8) | 20 (23.8) | <0.001 |
| Refused treatment | 7 (3.4) | 1 (0.8) | 6 (7.1) | 0.066 |
| Defaulted treatment | 20 (9.7) | 8 (6.5) | 12 (14.3) | 0.019 |
| Completed treatment | 132 (63.8) | 107 (87.0) | 25 (29.8) | <0.001 |
| Risk stratification | | | | <0.001 |
| High | 72 (34.8) | 28 (22.8) | 44 (52.4) | |
| Intermediate | 121 (58.5) | 92 (74.8) | 29 (34.5) | |
| Low | 3 (1.4) | 3 (2.4) | 0 (0) | |
| Not determined | 11 (5.3) | 0 (0) | 11 (13.1) | |
| Outcome | | | | |
| Lost to follow-up | 26 (12.6) | 18 (14.6) | 8 (9.5) | 0.3 |
| Relapsed | 42 (20.3) | 4 (3.3) | 38 (45.2) | <0.001 |
| Relapsed during treatment | 18 (42.9) | 2 (50.0) | 16 (42.1) | |
| Relapsed post-treatment | 18 (42.9) | 2 (50.0) | 16 (42.1) | |
| Relapsed after default | 6 (7.1) | 0 (0) | 6 (15.8) | |

*$p$-value for alive v. died determined by Pearson's $\chi^2$ test, Fisher's exact test or Wilcoxon rank sum test; $p<0.05$ = statistically significant difference between groups.

**Table 2. Comparison of medians and IQRs for total group, alive v. died and Lesotho v. SA patients (*N*=207)**

| Variable | Median (IQR) | Outcome | | |
|---|---|---|---|---|
| | | Alive (*n*=123), median (IQR) | Died (*n*=84), median (IQR) | *p*-value* |
| Age (months) | 38 (24 - 63) | 37 (24 - 63) | 41 (25 - 63) | 0.6 |
| Symptoms-to-diagnosis time (days) | 30 (10 - 60) | 21 (7 - 60) | 30 (16 - 90) | 0.007 |
| LDH level at diagnosis (U/L)† | 738 (137 - 494) | 710 (468 - 1 220) | 979 (547 - 1 736) | 0.002 |
| Time to chemotherapy (days) | 4 (2 - 6) | 4 (2 - 6) | 4 (2 - 7) | 0.7 |
| Time to refusal of treatment (days) | 20 (16 - 116) | 162 (162 - 162) | 19 (14 - 58) | 0.063 |
| Time to surgery (days) | 55 (45 - 63) | 50 (37 - 62) | 51 (32 - 70) | 0.066 |
| Time to relapse (days) | 294 (238 - 519) | 294 (268 - 490) | 295 (233 - 498) | 0.8 |
| Survival time (months) | 27 (9 - 82) | 66 (24 - 118) | 10 (2 - 18) | <0.001 |
| | | Country of residence | | |
| | | Lesotho (*n*=56) | SA (*n*=151) | |
| Age (months) | 38 (24 - 63) | 46 (34 - 63) | 34 (22 - 64) | 0.073 |
| Symptom-to-diagnosis time (days) | 30 (10 - 60) | 46 (21 - 90) | 25 (7 - 60) | 0.002 |
| LDH level at diagnosis (U/L)† | 738 (137 - 494) | 977 (565 - 1 778) | 749 (480 - 1 278) | 0.016 |
| Time to chemotherapy (days) | 4 (2 - 6) | 3 (2 - 6) | 4 (2 - 6) | 0.8 |
| Time to refusal of treatment (days) | 20 (16 - 116) | 10 (10 - 10) | 45 (19 - 130) | 0.3 |
| Time to surgery (days) | 55 (45 - 63) | 52 (38 - 76) | 49 (35 - 59) | 0.2 |
| Time to relapse (days) | 294 (238 - 519) | 334 (270 - 659) | 294 (223 - 412) | 0.2 |
| Survival time (months) | 27 (9 - 82) | 15 (5 - 43) | 35 (11 - 92) | 0.01 |

IQR = interquartile range; SA = South Africa.; LDH = lactate dehydrogenase.
*$p$-value for difference between groups determined by Pearson's $\chi^2$ test, Fisher's exact test or Wilcoxon rank sum test; $p<0.05$ = statistically significant difference between groups.
†Normal range for children 1 - 15 years: 143 - 370 U/L.[25]

**Table 3. Histological findings of risk categories in patients with nephroblastoma (*N*=207)**

| Category and histological type | *n* (% of total) | % of risk group |
|---|---|---|
| High risk | 12 (5.8) | - |
| Anaplastic | 7 (3.9) | 58.3 |
| Blastemal | 5 (2.4) | 41.7 |
| Intermediate risk | 159 (76.8) | - |
| Unspecified | 99 (47.8) | 62.3 |
| Regressive | 36 (17.4) | 22.6 |
| Mixed | 12 (5.8) | 7.5 |
| Stromal | 9 (4.3) | 5.7 |
| Epithelial | 2 (1.0) | 1.3 |
| Mesenchymal | 1 (0.5) | 0.6 |
| Low risk | 8 (3.9) | - |
| Necrotic | 8 (3.9) | 3.9 |
| Histology results unavailable | 28 (13.5) | - |
| Histology not performed | 25 (12.1) | 89.3 |
| Missing data | 3 (1.4) | 10.7 |

shown in Table 1, treatment refusal occurred in 3.4% (*n*=7) of cases, with a median (IQR) time of 20 (16 - 116) days after treatment initiation. Neo-adjuvant chemotherapy was administered to 196 (94.7%) patients, starting a median (IQR) of 4 (2 - 6) days after diagnosis (Tables 1 and 2). Surgery was performed on 180 (87.0%) patients, with a median (IQR) time to surgery of 50 (36 - 62) days (Tables 1 and 2). The outcomes of patients receiving neo-adjuvant chemotherapy are summarised in Table 1. Twenty-one (10.7%) patients had an unknown response, as they did not proceed to surgery. Of the 37 (17.9%) patients who received radiotherapy, 19 (51.4%) had stage IV disease, 17 (46.0%) stage III and 1 (2.7%) stage II disease.

## Outcome

Throughout the study period, 59.4% (*n*=123) of patients survived, with a median (IQR) survival rate of 27 (9 - 82) months (Table 2). A significant correlation was observed between survival and duration of symptoms ($p=0.007$), risk stratification ($p<0.001$), metastatic disease ($p<0.001$) and tumour burden (LDH level) ($p<0.002$), indicating decreasing survival with prolonged symptom duration and advancing disease stages.

Treatment was completed by 63.8% (*n*=132) of patients (Table 1), of whom 81.1% (*n*=107) survived. Survival was significantly higher among patients who completed treatment (81.1%) compared with non-completers (*n*=25/84; 29.8%; $p<0.001$). Twenty (9.7%) patients defaulted on their treatment and 26 (12.6%) were lost to follow-up, although no significant subsequent impact on survival was observed (Table 1).

Approximately one-fifth of patients relapsed (*n*=42; 20.3%), with a median (IQR) time from diagnosis to relapse of 294 (238 - 519) days (Tables 1 and 2), and mostly post treatment or during treatment (both *n*=18; 42.9%) (Table 1). Of the patients who relapsed, 92.9% (*n*=32/42) succumbed. Patients with disease relapse had a significantly higher mortality rate (45.2%) than those who survived (3.3%; $p<0.001$). Common relapse sites included the lungs (*n*=20/42; 47.6%), liver (*n*=12/42; 28.6%) and local tumour bed (*n*=13/42; 31.0%), among other areas (*n*=9/42; 21.4%).

Of the patients with local tumour bed relapses (*n*=13), 15.4% (*n*=2) had stage V (bilateral) disease with distant metastasis, leading to both kidneys being classified as stage IV. Tumours were categorised as stage IV in 30.8% (*n*=4/13) of patients, stage III in 23.1% (*n*=3/13), stage II in 7.7% (*n*=1), and stage I in 23.1% (*n*=3/13). Risk stratification included high risk in 46.2% (*n*=6/13) and intermediate risk in 53.8% (*n*=7/13) of patients. All these patients received neo-adjuvant chemotherapy and 92.3 % (*n*=12) responded well. The median (IQR) time to surgery was 55 (45 - 63) days, and 38.5% (*n*=5/13) received radiotherapy. Relapse occurred post treatment in

46.2% (*n*=6/13) of patients, during treatment in 46.2% (*n*=6/13) and after treatment default in 7.7% (*n*=1/13). The median (IQR) time to local tumour bed relapse was 288 (255 - 436) days. The mortality rate of these patients was 100% ($p<0.001$), with a median (IQR) survival time of 14 (10 - 28) months (Tables 1 and 2).

### Lesotho v. SA patients

Of the 151 SA patients, 79 (52.3%) were male, while 30 of the 56 (53.6%) Lesotho patients were female (Table 4). All Lesotho patients were black Africans. The SA patients' median (IQR) age was 34 (22 - 64) months, compared with Lesotho patients' 46 (34 - 63) months (Table 2).

SA patients had a median (IQR) symptom-to-diagnosis time of 25 (7 - 60) days, while Lesotho patients had a delay of 46 (21 - 90) days, a statistically significant difference ($p=0.002$) (Table 2). Delayed diagnosis (>2 weeks) affected 50.3% (*n*=76/151) of SA and 71.4% (*n*=40/56) of Lesotho patients ($p=0.03$). In both cohorts, the reason for the delay was often unknown (Lesotho *n*=21/40, 52.5%; SA *n*=34/76, 44.7%) (Table 4).

As summarised in Table 4, metastatic disease, response to chemotherapy, completion of treatment and risk stratification differed significantly between patients from the two countries, as did tumour load (Table 2). Staging significantly varied ($p=0.017$), with Lesotho patients having a higher stage IV prevalence (*n*=25/56; 44.6%) ($p=0.004$), while SA had more stage I cases (*n*=67/151; 44.3%) ($p=0.005$) (Table 4). Tables 2 and 4 summarise differences between SA and Lesotho patients regarding treatment and surgery rates, time to chemotherapy and surgery, completion of and response to chemotherapy. There was a significant difference ($p=0.02$) in chemotherapy response, with double the percentage of poor responses in Lesotho patients (31.4%, *n*=16/51) compared with SA patients (16.6%, *n*=24/145) (Table 4).

Patient outcomes were comparable (Table 4). At the end of the study period, 60.3% (*n*=91/151) of SA patients were alive, while 57.1% (*n*=32/56) of patients from Lesotho survived ($p=0.7$). The two countries had almost equal rates of patients who relapsed, and those who were lost to follow-up. However, the median (IQR) survival time differed significantly between the countries ($p=0.010$), with patients from SA (35 (11 - 92) months) surviving twice as long as Lesotho patients (15 (5 - 43) months) (Table 2).

### Factors associated with outcome

In the univariate analysis (Table 5), individuals categorised as high risk showed a significantly higher hazard of mortality (HR 2.89; 95% CI 1.88 - 4.45; $p<0.001$) than those in other risk groups. Patients with lung metastasis had an 85% higher hazard of mortality (HR 1.85; 95% CI 1.15 - 2.95; $p=0.010$) compared with metastasis to different locations. Additionally, individuals with metastasis to >1 site had a 2.56-fold higher mortality hazard (HR 2.56; 95% CI 1.32 - 4.97; $p=0.005$) than those with metastasis to a single site. Patients with histological features classified as anaplastic and blastemal had a 3.83 × higher hazard of death (HR 3.83; 95% CI 1.95 - 7.53; $p<0.001$) compared with other histological types, while patients with relapse had a 3.72 × higher hazard of death (HR 3.72; 95% CI 2.39 - 5.78; $p<0.001$) compared with patients who did not experience a relapse.

In the multivariate analysis (Table 5), after adjusting for variables such as metastasis to multiple sites, age at diagnosis and chemotherapy, only high-risk stratification and specific histological types were linked to increased mortality hazard. Those classified as high risk had an 88% higher hazard of mortality compared with other risk groups (adj. HR 1.88; 95% CI 1.02 - 3.45; $p=0.042$) after adjusting for metastasis to multiple sites, histology (anaplastic and blastemal), age at diagnosis, chemotherapy and relapse. As illustrated in Fig. 1, representing the adjusted Kaplan-Meier survival curve, we noted a statistically significant distinction in the survival of paediatric patients with nephroblastoma between high- and low-risk stratification from the time of diagnosis. Relapse was associated with a 4.14 × higher hazard of mortality compared to other types (adj. HR4.14; 95% CI 2.53 - 6.77; $p<0.001$) after accounting for metastasis to multiple sites, high-risk stratification, histology (anaplastic and blastemal), age at diagnosis and chemotherapy.

## Discussion

Early diagnosis and management of nephroblastoma poses a significant challenge in paediatric oncology worldwide. Our 21-year study at UAHC in SA aimed to understand nephroblastoma better, and provide insights into patient profiles, disease presentations, treatment approaches and outcomes. The findings emphasise the unique challenges faced by this medical facility due to limited resources and experience in referral areas, delayed presentations and socioeconomic disparities in the region. Our analysis revealed that high-risk stratification and relapse were associated with an increased hazard of mortality after adjusting for metastasis at multiple sites, histology (anaplastic and blastemal), age at diagnosis and chemotherapy.

Most of the study population was from the Free State province and Lesotho. We observed a marginally higher incidence among males (50.7%), contrary to international and local studies where females predominated.[7,26-29] Although the median age at diagnosis in this study (38 months) was younger than in other SA studies (42 - 45 months),[7,10] it aligned with multicentre international studies (38 - 39 months)[27,30] and a Nigerian study (36 months).[29] These age differences might also indicate variations in disease presentation across regions.

The patients' ethnicity in this study closely resembled that of the Free State province.[31] Most patients were black African (85.0%), which was similar to previous findings.[4,6-8,10] The low representation of white patients (5.3%) might be attributed to variations in health-seeking behaviour, as this group more commonly has access to private healthcare initially.[32,33]

The delay between symptom onset and diagnosis in this study (median 30 days) was concerning, surpassing reported durations in other studies (Tygerberg Hospital, SA, 5 - 20 days;[19] Egypt 8 - 28 days;[24] UK 7 days[34]), contributing to generally poorer outcomes.[19,24] The delay between symptoms and diagnosis in 56% of patients postponing seeking care and exceeding 90 days among patients who died underscores the urgent need for enhanced health literacy and improved healthcare accessibility.[7,24,32] Approximately 10% of referred patients facing delayed referral to UAHC received an incorrect initial diagnosis, a rate lower than observed in comparable studies (Tygerberg Hospital 58%;[19] Egypt 33%[24]). The reason for better diagnostic accuracy in our study could be delayed presentation with more advanced disease stages, making it easier to diagnose correctly the first time.

The tumour stage distribution revealed a comparable prevalence in stage I (38.6%) disease, with lower stages II (11.6%) and III (10.6%), compared with other SA studies.[7,10] However, we found a higher prevalence of stage IV (29.5%) disease, particularly among Lesotho patients (44.6%), which was similar to the advanced disease presentation reported in a Nigerian study,[29] prompting questions about factors contributing to this discrepancy. Despite no significant correlation between symptom duration and tumour stage, the increased prevalence of advanced disease at initial presentation suggests that relying solely on symptom duration might

**Table 4. Comparison between patients from Lesotho and SA**

| Variable | Total group (*n*=207) *n* (%) | Lesotho (*n*=56) *n* (%) | SA (*n*=151) *n* (%) | *p*-value* |
|---|---|---|---|---|
| Sex | | | | 0.5 |
| Male | 105 (50.7) | 26 (46.4) | 79 (52.3) | |
| Female | 102 (49.3) | 30 (53.6) | 72 (47.7) | |
| Ethnicity | | | | <0.001 |
| Black | 176 (85.0) | 56 (100) | 120 (79.5) | |
| White | 11 (5.3) | 0 (0) | 11 (7.3) | |
| Mixed race | 20 (9.7) | 0 (0) | 20 (13.2) | |
| Diagnosis | | | | |
| Delayed >2 weeks | 116 (56.0) | 40 (71.4) | 76 (50.3) | 0.03 |
| No reason | 55 (47.4) | 21 (52.5) | 34 (44.7) | 0.4 |
| Delayed seeking care | 21 (18.1) | 9 (22.5) | 17 (22.4) | >0.9 |
| Delayed referral | 26 (22.4) | 7 (17.5) | 14 (18.4) | >0.9 |
| Wrong initial diagnosis | 11 (9.5) | 1 (2.5) | 10 (13.2) | 0.094 |
| Passport problems | 2 (1.7) | 2 (5.0) | 0 (0) | 0.12 |
| Other | 1 (0.9) | 0 (0) | 1 (1.3) | >0.9 |
| Tumour side | | | | 0.2 |
| Unilateral (*n*=195) | 195 (94.2) | 55 (98.2) | 140 (92.7) | |
| Left | 100 (51.3) | 25 (44.6) | 75 (49.7) | |
| Right | 95 (48.7) | 30 (53.6) | 65 (43.0) | |
| Bilateral | 12 (5.8) | 1 (1.8) | 11 (7.3) | |
| Metastasis | 67 (32.4) | 26 (46.4) | 41 (27.2) | 0.008 |
| Site of metastasis (*n*=67) | | | | |
| Lungs | 46 (68.9) | 17 (30.4) | 29 (19.2) | 0.086 |
| Liver | 21 (31.3) | 11 (19.6) | 10 (6.6) | 0.006 |
| Inferior vena cava | 6 (9.0) | 3 (5.4) | 3 (2.0) | 0.3 |
| Bone marrow | 4 (6.0) | 1 (1.8) | 3 (2.0) | >0.9 |
| Stage | | | | 0.017 |
| I | 80 (38.6) | 13 (23.2) | 67 (44.4) | 0.005 |
| II | 24 (11.6) | 8 (14.3) | 16 (10.6) | 0.5 |
| III | 22 (10.6) | 7 (12.5) | 15 (9.9) | 0.6 |
| IV | 61 (29.5) | 25 (44.6) | 36 (23.8) | 0.004 |
| V | 11 (5.3) | 1 (1.8) | 10 (6.6) | 0.3 |
| Unstaged | 9 (4.3) | 2 (3.6) | 7 (4.6) | >0.9 |
| Treatment | | | | |
| Received neo-adjuvant chemotherapy | 196 (94.7) | 51 (91.1) | 145 (96.0) | 0.2 |
| Response to chemotherapy (*n*=196) | | | | 0.026 |
| Good | 135 (68.9) | 27 (52.9) | 108 (74.5) | |
| Poor | 40 (20.4) | 16 (31.4) | 24 (16.6) | |
| Unknown | 21 (10.7) | 8 (15.7) | 13 (9.0) | |
| Received surgery | 180 (87.0) | 46 (82.1) | 134 (88.7) | 0.2 |
| Received radiotherapy | 37 (17.9) | 12 (21.4) | 25 (16.6) | 0.4 |
| Refused treatment | 7 (3.4) | 1 (1.8) | 6 (4.0) | 0.7 |
| Defaulted treatment | 20 (9.7) | 9 (16.1) | 11 (7.3) | 0.057 |
| Completed treatment | 132 (63.8) | 29 (51.8) | 103 (68.2) | 0.029 |
| Risk stratification | | | | 0.042 |
| High | 72 (34.8) | 27 (48.2) | 45 (29.8) | |
| Intermediate | 121 (58.5) | 25 (44.6) | 96 (63.6) | |
| Low | 3 (1.4) | 0 (0) | 3 (2.0) | |
| Not determined | 11 (5.3) | 4 (7.1) | 7 (4.6) | |
| Outcome | | | | 0.7 |
| Alive | 123 (59.4) | 32 (57.1) | 91 (60.3) | |
| Died | 84 (40.6) | 24 (42.9) | 60 (39.7) | |
| Lost to follow-up | 26 (12.6) | 7 (12.5) | 19 (12.6) | >0.9 |
| Relapsed (*n*=42) | 42 (20.3) | 12 (21.4) | 30 (19.9) | 0.8 |
| Relapsed during treatment | 18 (42.9) | 4 (33.3) | 14 (46.7) | |
| Relapsed post-treatment | 18 (42.9) | 6 (50.0) | 12 (40.0) | |
| Relapsed after default | 6 (7.1) | 2 (16.7) | 4 (13.3) | |

SA = South Africa.
*$p$-value for Lesotho v. South African patients determined by Pearson's $\chi^2$ test, Fisher's exact test or Wilcoxon rank sum test; $p<0.05$, statistically significant difference between groups.

**Table 5. Factors associated with outcome in patients with nephroblastoma**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **HR** | **95% CI** | ***p*-value** | **Adj. HR** | **95% CI** | ***p*-value*** |
| Risk stratification: high risk | 2.89 | 1.88 - 4.45 | <0.001 | 1.88 | 1.02 - 3.45 | 0.042 |
| Metastasis site (multiple options) (choice: lungs) | 1.85 | 1.15 - 2.95 | 0.010 | - | - | - |
| Metastasis to >1 site | 2.56 | 1.32 - 4.97 | 0.005 | 1.55 | 0.67 - 3.61 | 0.3 |
| Histology (anaplastic and blastemal) | 3.83 | 1.95 - 7.53 | <0.001 | 2.10 | 0.92 - 4.80 | 0.078 |
| Age at diagnosis (months) | 1.00 | 1.00 - 1.01 | 0.60 | 0.99 | 0.99 - 1.00 | 0.11 |
| Chemotherapy | 1.39 | 0.82 - 2.36 | 0.22 | 1.39 | 0.81 - 2.38 | 0.2 |
| Relapse | 3.72 | 2.39 - 5.78 | <0.001 | 4.14 | 2.53 - 6.77 | <0.001 |

HR = hazard ratio; CI = confidence interval; adj. HR = adjusted hazard ratio.
*$p<0.05$ = statistically significant.

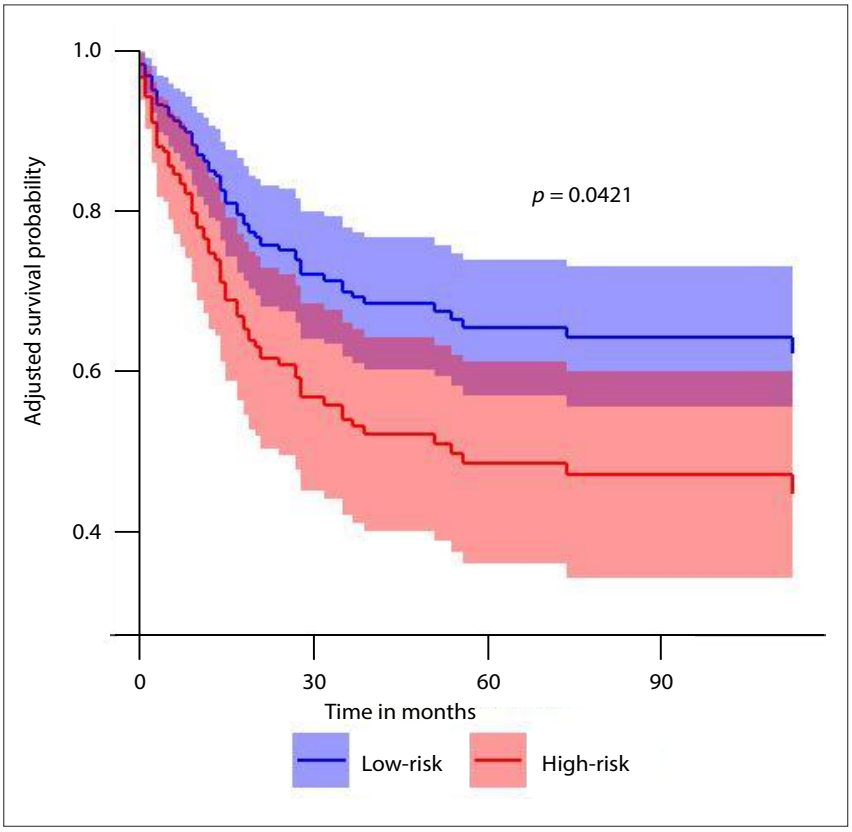


*Fig. 1. Adjusted Kaplan-Meier survival curve for relapse in paediatric patients with nephroblastoma.*

be an unreliable indicator. Furthermore, the multivariate analysis indicated that patients with high-risk stratification had an increased hazard of mortality, which corroborated findings from a previous study.[35]

Treatment dynamics in our study revealed patterns and challenges. Most (98.1%) patients were treated according to the modified SIOP protocol for African nations, aligning closely with recommended guidelines that focus on neo-adjuvant chemotherapy for most cases.[9] Despite following the same protocol, we identified a pronounced chemotherapy response difference between Lesotho (poor response 31.4%) and SA patients (poor response 16.6%), emphasising the need for customised strategies to enhance outcomes. Despite variable chemotherapy responses in our study cohort, there were lower treatment default rates in this study (9.7%) than reported in other sub-Saharan African countries (17.1% - 28.6%).[29,36] However, poor responses and treatment default remain a concern, warranting further investigation examining multifaceted factors, e.g. ignorance, belief in incurability, strong religious beliefs and socioeconomic considerations.[24,32,37]

Furthermore, our cohort's relapse rate (20.3%), although comparable with studies in other low- to middle-income countries (LMICs) (21% - 30%),[28,38] surpassed large multicentre studies (8.9% - 13%),[27,36,39] highlighting persistent challenges in sustaining long-term remission. The median time to relapse (294 days) was similar to previous findings.[27,38,40] Common relapse areas mirrored other studies,[25,34] with local tumour bed relapse rates (31.0%) corresponding with the literature (17.1%-53.3%),[28,36,38] suggesting meticulous surgical techniques during tumour resection. Our study's relapse-related mortality rate (45.2%) was in keeping with the literature (20% - 52%).[27,38,39] However, intensified surveillance and targeted interventions to enhance post-treatment outcomes remain a priority. The multivariate analysis showed that relapsing patients had an increased hazard of mortality, corroborating findings from a previous study.[41]

Although the 2-year overall survival rate of 59.4% in our study was comparable with other LMICs,[2,10,28] it lagged behind high-income countries.[2] Treatment default and death rates were in line with other LMICs,[27] while treatment refusal rates were low, and patients who completed treatment had similar survival rates to high-income countries.[27] Early-stage disease and early-diagnosed patients exhibited better survival rates, consistent with previous findings.[34] Lesotho patients generally performed worse due to advanced-stage disease and lower survival rates attributed to healthcare infrastructure limitations, delayed diagnoses and socioeconomic challenges in Lesotho.[42]

High-risk stratification, unfavourable histology and metastasis to the lung and to multiple sites had statistically significant increased mortality odds, which matched previous findings.[4,7,9,10,17, 27,29,38,39] The impact of these risk factors on mortality emphasises the importance of early tumour detection, treatment compliance, regular follow-up and continued research to refine treatment approaches.

## Study limitations

Reliance on patient files at UAHC, some of which had been destroyed, transferred, or lost over the 21-year study period, raised concerns about data completeness due to

missing information. Incomplete patient information, specifically regarding symptom history and reasons for delayed presentation, might have introduced bias when categorising patients who had a delayed diagnosis. Additionally, confounding factors such as HIV/AIDS[12] and nutritional deficiencies[43] were not investigated in this study, emphasising the need for future research to analyse these aspects thoroughly.

The authors propose the following recommendations: (*i*) implement community health education, increase access to primary care and streamline referrals to improve early detection and reduce delays; (*ii*) address socioeconomic barriers with financial support, train care providers to recognise early symptoms, promote screening for high-risk groups and enhance diagnostic infrastructure; and (*iii*) collaboration among healthcare providers, government and non-governmental organisations, along with continuous evaluation, is key to refining strategies and improving outcomes.

## Conclusion

In this study of 207 patients, mainly black and from SA or Lesotho, we found a median age at diagnosis of 38 months. Lesotho patients experienced more severe disease and longer diagnostic delays. Treatment completion was 63.8%, with 81.1% following protocols. Radiotherapy was given to 17.9% of patients with advanced disease. The overall survival rate was 59.4%, with a median survival of 27 months. Survival was linked to symptom duration, risk, metastasis and tumour burden. Improved cross-border healthcare collaboration between SA and Lesotho is needed to reduce delays and enhance outcomes.

This study emphasised the need for targeted interventions to address diagnostic delays and improve healthcare accessibility, especially in Lesotho. Strategies include enhancing health literacy, refining referral processes, minimising misdiagnoses and addressing socioeconomic barriers to reduce treatment default rates. Additionally, patients at risk of relapse should be fast-tracked to treatment. Future research should explore the reasons behind diagnostic delays, including cultural and regional variations in healthcare-seeking behaviour. Collaborative initiatives between healthcare providers in SA and Lesotho are essential to address these challenges comprehensively. A collaborative effort has the potential to shape tailored strategies, improve early detection, streamline treatment pathways and ultimately enhance outcomes for children with nephroblastoma.

This 21-year study on nephroblastoma at UAHC revealed unique challenges. Noteworthy observations on patient demographics, diagnostic delays, tumour stage distribution and treatment dynamics revealed regional variations, emphasising the need for targeted interventions. Future research should analyse confounding factors to gain a more comprehensive understanding of the complexities of nephroblastoma.

**Data availability.** Data are available from the corresponding author upon reasonable request.

**Declarations.** The research for this study was done in partial fulfilment of the requirements for the student researchers' MB ChB degree at the University of the Free State, Bloemfontein, SA.

**Acknowledgements.** Ms Theanette Mulder and Dr Daleen Struwig, medical editors/writers, Faculty of Health Sciences, University of the Free State, for technical and editorial preparation of the manuscript.

**Author contributions.** EG, II, LM, JW, SD, PN, SS and AM developed the study protocol, collected the data and prepared the initial manuscript draft. JBS performed the statistical analysis of data. EB was the study supervisor, suggested the concept and assisted with protocol development, interpretation of data and manuscript preparation, and wrote the final draft of the article. All the authors approved the final version of the article.

**Funding.** None.

**Conflicts of interest.** None.

1. Popov SD, Sebire NJ, Vujanic GM. Wilms tumor – histology and differential diagnosis. In: Van den Heuvel-Eibrink MM, ed. Wilms' Tumour. Singapore: Codon Publications, 2016. https://exonpublications.com/index.php/exon/article/view/96/122 (accessed 11 April 2024).
2. Cunningham ME, Klug TD, Nuchtern JG, et al. Global disparities in Wilms tumor. J Surg Res 2020;247:34-51. https://doi.org/10.1016/j.jss.2019.10.044
3. World Health Organization. WHO Report on cancer: Setting priorities, investing wisely and providing care for all. Geneva: WHO, 2020. https://www.who.int/publications/i/item/9789240001299 (accessed 11 April 2024).
4. 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
5. Stefan C, Bray F, Ferlay J, Liu B, Maxwell Parkin D. Cancer of childhood in sub-Saharan Africa. Ecancermedicalscience 2017;11:755. https://doi.org/10.3332/ecancer.2017.755
6. Stefan D. Epidemiology of childhood cancer and the SACCSG tumour registry. Contin Med Educ 2010;28(7);317-319. http://www.cmej.org.za/index.php/cmej/article/view/1837/1548 (accessed 11 April 2024).
7. Visser YT, Uys R, van Zyl A, Stefan DC. Nephroblastoma – a 25-year review of a South African unit. J Med Life 2014;7(3):445-449. https://scholar.sun.ac.za/items/9ebcdad5-e65f-48e6-bbe3-376b3e4aa54c (accessed 11 April 2024).
8. Davidson A, Hartley P, Desai F, Daubenton J, Rode H, Millar A. Wilms tumour experience in a South African centre. Pediatr Blood Cancer 2006;46(4):465-471. https://doi.org/10.1002/pbc.20388
9. Israels T, Pidini D, Borgstein E, et al. Survival of children with a Wilms tumor in Blantyre, Malawi. Pediatr Hematol Oncol 2018;35(3):196-202. https://doi.org/10.1080/08880018.2018.1498564
10. Stones DK, Hadley GP, Wainwright RD, Stefan DC. The impact of ethnicity on Wilms tumor: Characteristics and outcome of a South African cohort. Int J Pediatr 2015:706058. https://doi.org/10.1155/2015/706058
11. Paintsil V, David H, Kambugu J, et al. The Collaborative Wilms Tumour Africa Project; baseline evaluation of Wilms tumour treatment and outcome in eight institutes in sub-Saharan Africa. Eur J Cancer 2015;51(1):84-91. https://doi.org/10.1016/j.ejca.2014.10.030
12. Hadley LG, Rouma BS, Saad-Eldin Y. Challenge of pediatric oncology in Africa. Semin Pediatr Surg 2012;21(2):136-141. https://doi.org/10.1053/j.sempedsurg.2012.01.006
13. Howard SC, Zaidi A, Cao X, et al. The My Child Matters programme: Effect of public-private partnerships on paediatric cancer care in low-income and middle-income countries. Lancet Oncol 2018;19(5):e252-e266. https://doi.org/10.1016/S1470-2045(18)30123-2
14. Wilde JC, Lameris W, van Hasselt EH, Molyneux EM, Heij HA, Borgstein EG. Challenges and outcome of Wilms' tumour management in a resource-constrained setting. Afr J Paediatr Surg 2010;7(3):159-162. https://doi.org/10.4103/0189-6725.70416
15. Njuguna F, Martijn HA, Kuremu RT, et al. Wilms tumor treatment outcomes: Perspectives from a low-income setting. J Glob Oncol 2016;3(5):555-562. https://doi.org/10.1200/JGO.2016.005389
16. Kanyamuhunga A, Tuyisenge L, Stefan DC. Treating childhood cancer in Rwanda: the nephroblastoma example. Pan Afr Med J 2015;21:326. https://doi.org/10.11604/pamj.2015.21.326.5912
17. Atanda AT, Anyanwu LJ, Atanda OJ, Mohammad AM, Abdullahi LB, Farinyaro AU. Wilms' tumour: Determinants of prognosis in an African setting. Afr J Paediatr Surg 2015;12(3):171-176. https://doi.org/10.4103/0189-6725.170185
18. Abdallah FK, Macharia WM. Clinical presentation and treatment outcome in children with nephroblastoma in Kenya. East Afr Med J 2001;78(7 Suppl):S43-47. https://ecommons.aku.edu/cgi/viewcontent.cgi?article=1076&context=eastafrica_fhs_mc_paediatr_child_health (accessed 11 April 2024).
19. Stefan DC, Siemonsma F. Delay and causes of delay in the diagnosis of childhood cancer in Africa. Pediatr Blood Cancer 2011;56(1):80-85. https://doi.org/10.1002/pbc.22714
20. Brits E, le Grange SM. Biliary atresia: the profile, management and outcome of patients treated at a tertiary hospital in central South Africa. S Afr Med J 2023;113(11):57-26. https://doi.org/10.7196/SAMJ.2023.v113i11.845
21. Arnold R, Khokho K, Narrainsamy K, Brits E, Joubert G. Infantile hypertrophic pyloric stenosis: profile, management and outcome of patients admitted to a tertiary hospital in Bloemfontein, South Africa. S Afr J Surg 2019;57(2):64. https://doi.org/10.17159/2078-5151/2019/v57n2a2811
22. Du Preez H, Brits E. The profile and outcome of small bowel atresia at Universitas Academic Hospital. S Afr J Surg 2023;61(1):61-65. https://doi.org/10.36303/SAJS.329
23. Brits E, le Grange. Perineal disintegration syndrome (PDS) in children with human immunodeficiency virus (HIV) infection: A scoping review. J Pediatr Surg 2024;59(11):161631. https://doi.org/10.1016/j.jpedsurg.2024.07.016
24. Abdelkhalek E, Sherief L, Kamal N, Soliman R. Factors associated with delayed cancer diagnosis in egyptian children. Clin Med Insights Pediatr 2014;8:39-44. https://doi.org/10.4137/CMPed.S16413
25. University of Rochester Medical Centre. Lactate dehydrogenase (blood). University of Rochester Medical Centre , 2024. https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=lactic_acid_dehydrogenase_blood (accessed 24 April 2024).
26. Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms tumor. Med Pediatr Oncol 1993;21(3):172-181. https://doi.org/10.1002/mpo.2950210305
27. Brok J, Lopez-Yurda M, Tinteren HV, et al. Relapse of Wilms' tumour and detection methods: A retrospective analysis of the 2001 Renal Tumour Study Group – International Society of Paediatric Oncology Wilms' tumour protocol database. Lancet Oncol 2018;19(8):1072-1081. https://doi.org/10.1016/S1470-2045(18)30293-6
28. Chagaluka G, Paintsil V, Renner L, et al. Improvement of overall survival in the Collaborative Wilms Tumour Africa Project. Pediatr Blood Cancer 2020;67(9):e28383. https://doi.org/10.1002/pbc.28383
29. Nasir AA, Abdur-Raheem NT, Abdur-Rahman LO, et al. Characteristics and clinical outcomes of children with Wilms' tumour: A 15-year experience in a single centre in Nigeria. J Pediatr Surg 2024;95(5):1009-1014. https://doi.org/10.1016/j.jpedsurg.2023.12.018
30. Wang J, Li M, Tang D, Gu W, Mao J, Shu Q. Current treatment for Wilms tumor: COG and SIOP standards. World J Pediatr Surg 2019;2(3):e000038. https://doi.org/10.1136/wjps-2019-000038
31. Statistics South Africa. Mid-year population estimates, 2019. Pretoria: Statistics South Africa, 2019. https://www.statssa.gov.za/publications/P0302/P03022019.pdf (accessed 11 April 2024).
32. Statistics South Africa (2013) Use of health facilities and levels of selected health conditions in South Africa: findings from the General Household Survey, 2011. Pretoria: Statistics South Africa. https://www.statssa.gov.za/publications/Report-03-00-05/Report-03-00-052011.pdf. (accessed 11 April 2024).
33. Abera Abaerei A, Ncayiyana J, Levin J. Health-care utilization and associated factors in Gauteng province, South Africa. Glob Health Action 2017;10(1):1305765. https://doi.org/10.1080/16549716.2017.1305765

34. Pritchard-Jones K, Graf N, van Tinteren H, Craft A. Evidence for a delay in diagnosis of Wilms' tumour in the UK compared with Germany: implications for primary care for children. Arch Dis Child 2016;101(5):417-420. https://doi.org/10.1136/archdischild-2015-309212
35. Dome JS, Perlman EJ, Graf N. Risk stratification for Wilms tumor: Current approach and future directions. Am Soc Clin Oncol Educ Book 2014:215-223. https://doi.org/10.14694/EdBook_AM.2014.34.215
36. Yao AJ, Moreira C, Traoré F, et al. Treatment of Wilms tumor in sub-Saharan Africa: Results of the Second French African Pediatric Oncology Group Study. J Glob Oncol 2019;5:1-8. https://doi.org/10.1200/JGO.18.00204
37. Friedrich P, Lam CG, Kaur G, Itriago E, Ribeiro RC, Arora RS. Determinants of treatment abandonment in childhood cancer: results from a global survey. PLoS ONE 2016;11(10):e0163090. https://doi.org/10.1371/journal.pone.0163090
38. Zekri W, Yacoub DM, Ibrahim A, Madney Y. Relapsed Wilms' tumor in pediatric patients: Challenges in low- to middle-income countries-a single-center experience. J Egypt Natl Canc Inst 2020;32(1):21. https://doi.org/10.1186/s43046-020-00032-6
39. Reinhard H, Schmidt A, Furtwängler R, et al. Outcome of relapses of nephroblastoma in patients registered in the SIOP/GPOH trials and studies. Oncol Rep 2008;20(2):463-467. https://doi.org/10.3892/or_00000029
40. South African Children's Cancer Study Group. South African Children's Tumour Registry. SACCSG, 2024. http://saccsg.co.za/SACTRegistry (accessed 11 April 2024).
41. Cotterill SJ, Pearson AD, Pritchard J, et al. Clinical prognostic factors in 1277 patients with neuroblastoma: Results of the European Neuroblastoma Study Group 'Survey' 1982 - 1992. Eur J Cancer 2000;36(7):901-908. https://doi.org/10.1016/S0959-8049(00)00058-7
42. World Bank. Lesotho: Public health sector expenditure review. Washington, DC: World Bank Group, 2017. http://documents.worldbank.org/curated/en/311321517929746662/Lesotho-public-health-sector-expenditure-review (accessed 11 April 2024).
43. Draper KS, Hadley GP, Pillay K, Wiles NL. Relationship between nutritional status and treatment-related neutropenia in children with nephroblastoma. S Afr J Clin Nutr 2018;31(4):74-77. https://doi.org/10.1080/16070658.2017.1401289

*Received 13 May 2024; accepted 30 August 2024.*