Age at diagnosis as a prognostic factor in South African children with neuroblastoma

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ABSTRACT

***Purpose*:** Low- and middle-income countries (LMICs) reported a higher median age at diagnosis of neuroblastoma (NB) compared to high-income countries. The aim was to determine if the optimal age at diagnosis, which maximizes the difference in overall survival between younger versus older patients in the South African population was similar to the internationally validated 18 months age cut-point.

***Methods*:** Four hundred sixty NB patients diagnosed between 2000 and 2016 were included. Receiver operating characteristic (ROC) curves were used to predict potential age cut-point values for overall survival in all risk group classifications. Risk ratios, sensitivity, specificity, and positive and negative predictive values at the specific cut-points were estimated with 95% confidence intervals, and time to mortality by age at the specific cut-points was shown with Kaplan-Meier curves and compared using log-rank tests.

Results: The median age at diagnosis for the total cohort was 31.9 months (range 0.2-204.7). For high-risk (HR), intermediate-risk, low-risk, and very low-risk patients, the median age at

diagnosis was, respectively, 36 months (range 0.4-204.7), 16.8 months (range 0.7-145.1), 14.2 months (range 2.0-143.5), and 8.7 months (range 0.2-75.6). The ROC curves for the total NB cohort (area under the curve [AUC] 0.696; $P < .001$) and HR (AUC 0.682; $P < .001$) were analyzed further. The optimal cut-point value for the total cohort was at 19.1 months (sensitivity 59%; specificity 78%). The HR cohort had potential cut-point values identified at 18.4 months age at diagnosis (sensitivity 45%; specificity 87%) and 31.1 months (sensitivity 67%; specificity 62%). The 19.1 months cut-point value in the total cohort and the 18.4 months cut-point value in HR were as useful in predicting overall survival as 18 months age at diagnosis.

Conclusion: The 18 months cut-point value appears to be the appropriate age for prognostic determination, despite the higher median age at diagnosis in South Africa.

Keywords: age of diagnosis, low- and middle-income country, neuroblastoma, prognostic factor

ABBREVIATIONS

- AUC - area under the curve
- COG - Children's Oncology Group
- HIC -high-income countries
- HR - high risk
- INRG - International Neuroblastoma Risk Group
- IR - intermediate risk
- LMIC - low- and middle-income countries
- LR - low risk
- NB - neuroblastoma
- NPV - negative predictive value
- OS - overall survival
- POU - pediatric oncology units
- PPV - positive predictive value
- ROC - receiver operating characteristic curve
- RR - risk ratio
- SIOP - International Society for Paediatric Oncology
- VLR - very low risk

1 INTRODUCTION

Neuroblastoma (NB) is a sympathetic tumor presenting mainly in childhood with a median age at diagnosis of 19 months.[1, 2] The majority of children are diagnosed under 5 years of age.[1] Age at diagnosis is an important risk factor in all international NB risk classification systems that predict the prognosis and influence the intensity of treatment. These include the Children's Oncology Group (COG) risk classification system, International Neuroblastoma Risk Group (INRG) staging system, and the International Society for Paediatric Oncology - Paediatric Oncology for Developing Countries (SIOP-PODC) guidelines for the treatment of NB in low- and middle-income countries (LMIC).[2-4] The prognostic effect of age at diagnosis is evident by an almost 90% 5-year overall survival (OS) in children diagnosed under 1 year of age compared to 52% in children diagnosed older than 5 years of age at diagnosis.[5]

Although the prognostic contribution of age is a continuum, the original age cut-off that predicted a binary outcome was 1 year.[6] While Shimada et al introduced an 18-month age cut-point in the definition of international neuroblastoma pathology classification (INPC) to predict unfavorable histology,[7] it were Breslow and McCann who first proposed using age as a prognostic factor with an 18-month cut point.[6] Subsequently, multivariate analysis with clinically significant factors including stage, histology, and MYCN-amplification, a cut-point value of 18 months remained of prognostic significance, and 18-20 months was determined as an acceptable range.[8]

These established binary cut-point values were based on studies that were conducted in high-income countries (HIC).[8] There are limited data available from LMIC, where the median age at diagnosis ranged from 24 to 48 months in Thailand, Iran, and Egypt, with 5-year OS that ranged from less than 10% to 48%.[9-11] We hypothesized that the South African population would follow similar LMIC trends and that the delayed median age at diagnosis (compared to HIC) would have prognostic significance. The aims of this study were threefold: the first aim was to estimate the median age at diagnosis in South Africa. The second aim was to identify a potential cut-point value for the age of diagnosis with OS as a primary endpoint in the South African population. The third aim was to evaluate whether the determined potential cut-point value and median age at diagnosis in the South African population was similar to the established 18 months international age cut-point value for prognosis. Thereby, a possible optimal cut-point value for the age at diagnosis could be identified for the South African population.

2 MATERIALS AND METHODS

A total of 460 children were diagnosed with NB in nine dedicated pediatric oncology units (POUs) in South Africa between January 2000 and December 2016. POUs were invited to participate in the study on a voluntary basis and the nine POUs represented all the regions of South Africa. The documented date of birth for each patient corresponded to the age stated on their birth certificates. Age at diagnosis was calculated as the period between the date of birth and the date of tumor biopsy, bone marrow aspiration, or raised urinary catecholamine levels, if biopsy was not possible. Patients were clinically and radiologically restaged according to the INRG classification system (Appendix S1A).[12] The OS time was defined as the period from diagnosis to death or date last seen. The potential cut-point values were defined as the points that classified most of the individuals correctly with the "point closest-to-(0.1) corner" method in the receiver operating characteristic (ROC) curve plane or the point with the smallest Euclidean distance between the ROC curve and the (0.1) point.[13] The sensitivity refers to the proportion of patients diagnosed under the cut-point age who were still alive. The specificity refers to the portion of patients over the cut-point age who were dead.[14] For the study, a high sensitivity was prioritized in the evaluation for the OS. An optimal cut-point value was defined as a statistically significant cut-point value with the highest sensitivity as determined by the "point closest-to-(0.1)" method on the ROC curve.

The risk ratio or relative risk (RR) was interpreted as the ratio of the risk of death in those diagnosed above the cut-point age to the risk of death of those diagnosed under the cut point age on the ROC curves.[15] The hazard ratio was defined as the instantaneous event rates of older patients (diagnosed above the cut-point age) compared to younger patients (diagnosed below the cut-point age).[15] The Faculty of Health Sciences Research Ethics Committee of Stellenbosch University (S18/07/138) approved the study.

2.1 Statistical analysis

Data were analyzed using IBM SPSS version 25 (IBM Corporation, NY) statistical software, and EpiCalc was used to determine predictive values for survival.[16, 17] Since the high-risk (HR) cohort constituted a significant proportion of the total cohort, the study aims were applied to both the total study cohort and the HR cohort. The median age and age range for the cohorts were calculated from demographic data. ROC curves, with age as a continuous variable, were constructed for the purpose of identifying optimal cut-point values and estimating the sensitivities (true positive rate) and specificities (false positive rate) of the age at diagnosis against OS at several cut-point values.[18] The usefulness of the ROC curves was evaluated by the size of the area under the curve (AUC). AUC values between 0.7 and 0.8 identified age cut-points that were deemed acceptable to be able to discriminate between patients who died and those who did not, while AUCs of 0.5 or less were unable to perform this discrimination.[19] The "point closest-to-(0.1) corner" method was used to identify the potential cut-point values for both the total cohort and the HR cohort. A Cox proportional hazards model was used to estimate HR and 95% confidence interval (CI) at each potential cut-point age. Kaplan-Meier curves and log-rank tests in the total cohort (all risk groups) and the HR cohort separately visualized time to event for different age cut-points. There were survival data available for 442 patients in the total cohort and 346 patients in the HR cohort. The 95% CIs of both the sensitivities and specificities for the potential cut-point values were compared to those of the internationally validated 18-month age at diagnosis to evaluate if the optimal cut-point values had similar prognostic value to the 18-month cut point.

Cut-point values for the age of diagnosis were determined at the sensitivity increments of 10%. Thereafter, the cut-point values were evaluated by using log-rank tests. The sensitivities, specificities, RRs, and positive and negative predictive values (NPVs) for all potential cut-point values were determined to evaluate the overlap of CIs. The chi-square test was used to test the association between age at different cut-points and the occurrence of death as a binary endpoint. The log-rank test was used to compare time-to-mortality at different cut-points for OS. *P*-values of less than .05 indicated statistical significance.

3 RESULTS

There was a male predominance with a male to female ratio of 1:0.92 for the 460 included patients. The median age at diagnosis for the total cohort was 31.9 months (range 0.2-204.7) (Table 1 and Figure 1). There were 179 patients (38.9%) diagnosed before 2 years and 369 (80.0%) within 5 years. The remaining 19.9% were diagnosed older than age 5 years. The HR group contributed 354 (77.0%) patients with a median age of 36 months (range 0.4-204.7). Intermediate-risk (IR; n = 36; 7.8%), low-risk (LR; n = 30; 6.5%), and very low-risk (VLR; n = 18; 3.9%) groups had median ages of 16.8 months (range 0.7-145.1), 14.2 months (range 2.0-143.5), and 8.7 months (range 0.2-75.6), respectively. Twenty-two (4.8%) patients could not be classified. This group had a median age of 15.6 months and a range of 0.4-108.

TABLE 1. The age at diagnosis according to INRG classification system in a cohort of 460 children with neuroblastoma in South Africa

	n (%)	Median (months)	Range (months)
Total cohort	460	31.9	0.2-204.7
HR cohort	354 (77.0)	36.0	0.4-204.7
IR cohort	36 (7.8)	16.8	0.7-145.1
LR cohort	30 (6.5)	14.2	2.0-143.5
VLR cohort	18 (3.9)	8.7	0.2-75.6
Unclassified	22 (4.8)	15.6	0.4-108

Abbreviations: HR, high risk; INRG, international neuroblastoma risk group; IR, intermediate risk; LR, low risk; VLR, very low risk.

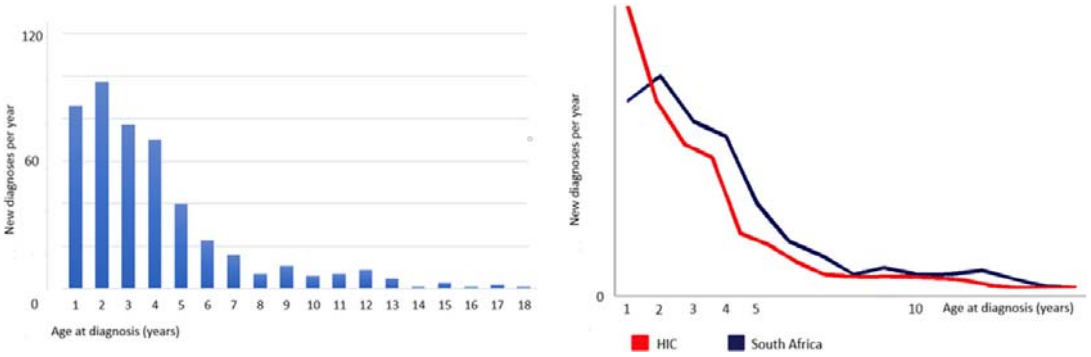

FIGURE 1. The distribution of the total South African neuroblastoma age at diagnosis cohort compared to high-income countries (HIC)

Using age at diagnosis as a continuous variable to predict OS, the area under the ROC curve for the total cohort was 0.696 (0.633-0.759; $P < .001$) and 0.682 (0.594-0.770; $P < .001$) for the HR cohort (Table 2), thus acceptable for evaluation purposes. The cohorts for IR, LR, and VLR were too small for valid ROC curve analysis. When evaluating the sensitivity and specificity coordinates for both the total cohort and the HR cohort, the sensitivities increased with increasing age at diagnosis, whilst the specificity decreased (Table 3).

TABLE 2. ROC curve's AUC for the age at diagnosis as a continuous variable[18]

	N (%)	AUC	SE	*P*-value	95% CI on AUC	
					Lower limit	**Upper limit**
Total cohort	460	0.696	0.032	<.001	0.633	0.759
HR cohort	354 (77.0)	0.682	0.045	<.001	0.594	0.770

Note. References for the usefulness of the ROC curves - AUC 0.5: no discrimination/inability to use as measure; 0.7-0.8: acceptable; 0.8-0.9: excellent; >0.9: outstanding.

Abbreviations: AUC, area under the curve; CI, confidence interval; HR, high risk; ROC, receiver operating characteristic.

TABLE 3. Cut-points for age at diagnosis, sensitivity, and specificity determined on the ROC curves

Total cohort (all risk groups), n = 460 (100%)						
Age at diagnosis (months)	**Se% (95% CI)**	**Sp% (95% CI)**	**RR (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	***P*-value***
18.0	55% (45, 65)	81% (77, 85)	3.41 (2.44, 4.76)	0.46 (0.37, 0.55)	0.87 (0.82, 0.90)	<.001
19.1	59% (49, 69)	80% (76, 84)	3.64 (2.59, 5.12)	0.47 (0.38, 0.55)	0.87 (0.83, 0.91)	<.001
27.3	70% (60, 79)	61% (56, 66)	2.82 (1.92, 4.14)	0.34 (0.28, 0.41)	0.88 (0.83, 0.92)	<.001
43.9	80% (71, 87)	35% (30, 40)	1.85 (1.18, 2.89)	0.26 (0.21, 0.31)	0.86 (0.79, 0.91)	.005
67.7	90% (82, 95)	18% (14, 23)	1.77 (0.97, 3.24)	0.24 (0.20, 0.28)	0.87 (0.76, 0.93)	.049
HR cohort, **n = 354 (77.0%)**						
Age at diagnosis (months)	**Se% (95% CI)**	**Sp% (95% CI)**	**RR (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	***P*-value***
18.0	46% (31, 61)	88% (83, 91)	4.2 (2.53, 6.98)	0.36 (0.24, 0.49)	0.92 (0.88, 0.94)	<.001
18.4	48% (33, 63)	86% (82, 90)	4.08 (2.44, 6.80)	0.34 (0.23, 0.47)	0.92 (0.88, 0.94)	<.001
27.1	61% (45, 75)	66% (60, 71)	2.58 (1.49, 4.49)	0.21 (0.15, 0.29)	0.92 (0.87, 0.95)	.001
31.1	71% (61, 80)	58% (52, 63)	2.62 (1.77, 3.86)	0.32 (0.26, 0.39)	0.88 (0.83, 0.91)	.001
38.3	72% (56, 84)	48% (43, 54)	2.14 (1.17, 3.93)	0.17 (0.12, 0.23)	0.92 (0.86, 0.95)	.011
43.8	78% (63, 89)	37% (32, 43)	1.94 (1.00, 3.78)	0.16 (0.11, 0.21)	0.92 (0.85, 0.96)	.047

Abbreviations: HR, high risk; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; RR, risk ratio; Se, sensitivity; Sp, specificity.

* *P*-values for sensitivity and specificity calculations at the cut-points for age at diagnosis were assessed by chi-square test.

3.1 Determining cut-point values with ROC curves

The ROC curves for the total cohort (all risk classifications) are presented in Figure 2 and the HR cohort in Figure 3. The sensitivity of each age was determined at several specificity levels. Selected sensitivities at the current international standardized prognostic age at diagnosis of 18 months and sensitivities at selected age of diagnosis representing increments of 10% were determined. These cut-point values on the ROC curves in Figures 2 and 3 are given in Table 3.

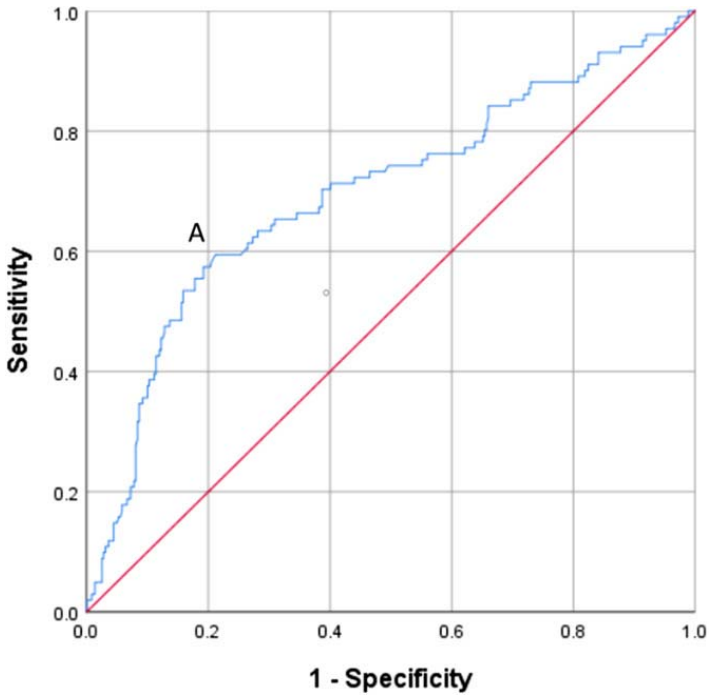

FIGURE 2. Receiver operating characteristic (ROC) curve for the age at diagnosis in all neuroblastoma risk groups in South Africa between 2000 and 2016 ($P < .001$)

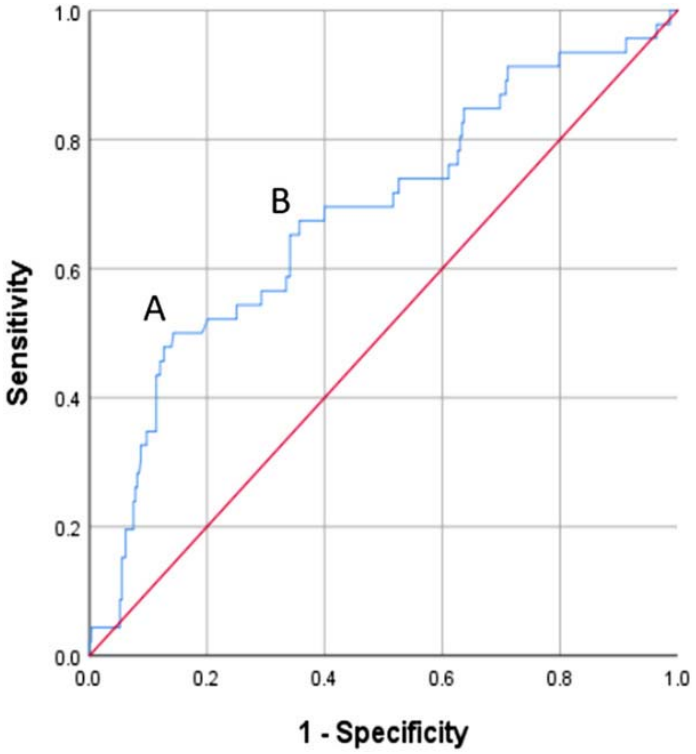

FIGURE 3. Receiver operating characteristic (ROC) curve for the age at diagnosis in the high-risk (HR) neuroblastoma group in South Africa between 2000 and 2016 ($P < .001$)

The total cohort had an optimal age at diagnosis cut-point value at 19.1 months, which yielded a sensitivity of 59% and specificity of 78% (Figure 2, point A). The HR cohort had two optimal cut-point values at 18.4 months, sensitivity of 45% and specificity of 87% (Figure 3, point A); and 31.1 months, sensitivity of 67% and specificity of 62% (Figure 3, point B).

3.2 RR and predictive values of the cut-points

When considering RR for the determined ROC curve cut-point values for the total cohort and HR cohort, the RR was the highest at 19.1 months for the total cohort (RR = 4.7). In the HR cohort, the highest RR was at 18 months (RR = 4.2) (Table 3). For the 18-month cut-off, the positive predictive value (PPV, interpreted as the percentage of those who were diagnosed at an age younger than the cut point who survived) for survival and NPV (interpreted as the percentage of those who were diagnosed at an age older than the cut point who died) were the highest for both the total cohort (PPV 36%; NPV 92%) and the HR cohort (PPV 36%; NPV 92%) (Table 3).

3.3 Determining OS at the optimal cut-point value

We determined the OS outcomes at the potential ROC curve cut-point values for both the total cohort (Figure 2, point A) and the HR cohort (Figure 3, points A and B). To determine the significance of OS, we estimated the *P*-values and quantified the effect by determining hazard ratios for the relevant cut-point values.

3.3.1 For the total cohort

At the ROC curve potential cut-point value point A (sensitivity 59%; specificity 78%; age at diagnosis of 19.1 months) (Figure 2), the difference in OS between the two age groups (hazard ratio 2.0), as illustrated by the Kaplan-Meier curve at 18 months, appears to be similar to the potential cut-point value ($P < .001$) (Figure 4). Therefore, point A conforms to our definition of an optimal cut-point value.

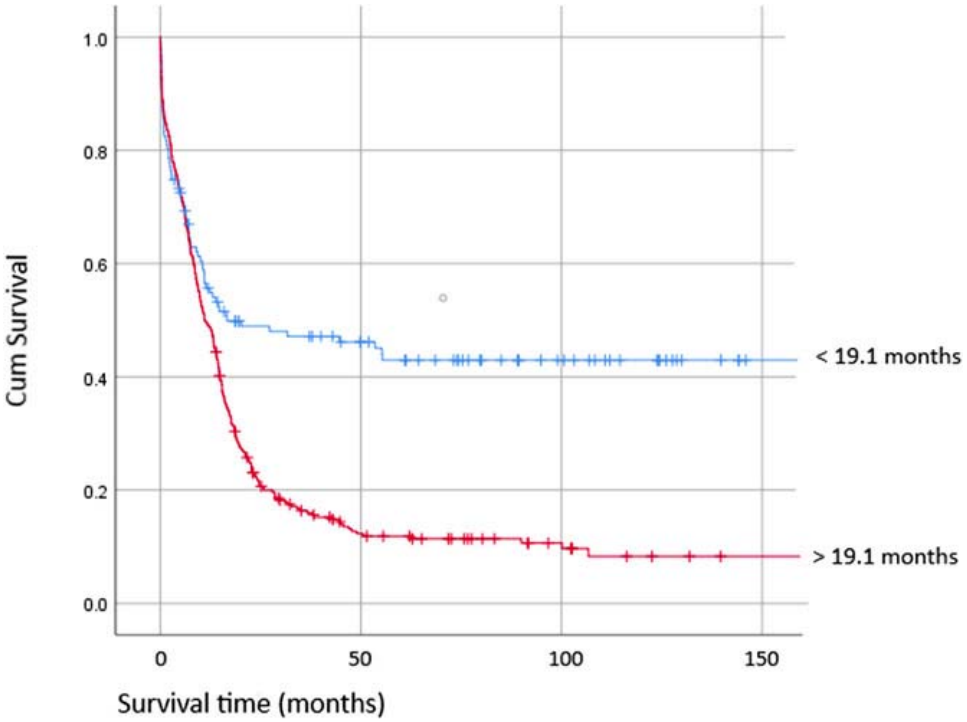

FIGURE 4. Kaplan-Meier curves for overall survival (OS) of age at diagnosis of 19.1-month cut-point value for the total neuroblastoma cohort ($P < .001$)

3.3.2 For the HR cohort

At the ROC curve potential cut-point value A (sensitivity 45%; specificity 87%; age at diagnosis of 18.4 months), the difference in OS between the two age groups (hazard ratio 1.9), as illustrated by the Kaplan-Meier curve at 18 months, appears to be similar to the 18.4-month potential cut-point value ($P < .001$) (Figure 5). Therefore, point A conforms to our definition of an optimal cut-point value. At the ROC curve potential cut-point value point B (sensitivity 67%; specificity 62%; age at diagnosis of 31.1 months) was not statistically significant ($P = .178$), and therefore did not meet our definition for an optimal cut-point value in the South African HR cohort.

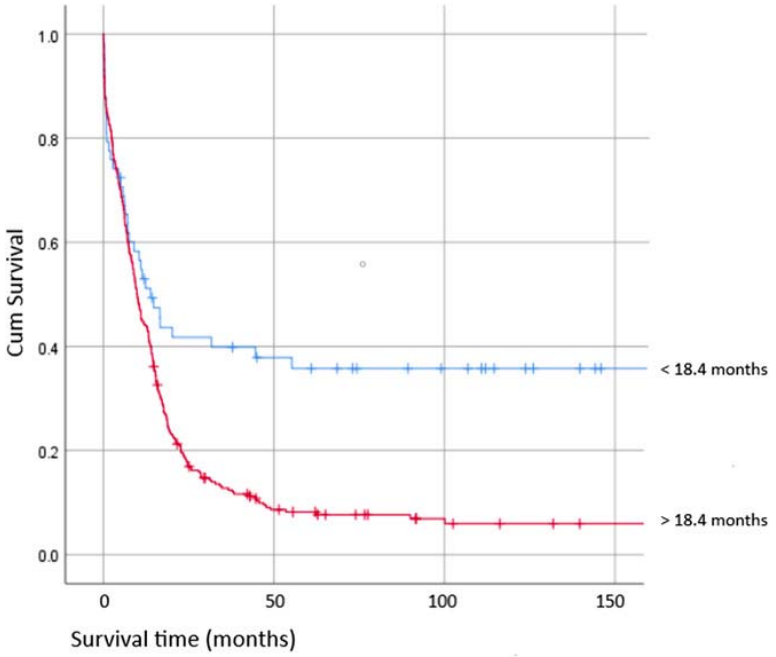

FIGURE 5. Kaplan-Meier curves for overall survival (OS) of age at diagnosis of 18.4-month cut-point value in high-risk (HR) neuroblastoma ($P < .001$)

3.3.3 For both the total cohort and HR cohort

The sensitivities, specificities, RR, PPV, and NPV including their respective 95% CIs of the 19.1-month cut-point value of the total cohort as well as the 18.4-month cut-point value of the HR appeared to be similar to those of the international validated 18-month cut-point values (Table 3). There is large degree of overlap of the 95% CIs for the 18.0- and 19.1-month cut-point values of the total cohort as well as the 18.0- and 18.4-month cut-point values of the HR cohort.

4 DISCUSSION

In various studies, age, stage, and biological factors have individually and in multivariate analysis been shown to have prognostic significance in NB.[2] North American studies reported the median age at diagnosis as 19 months (range 12-20), while German studies reported median age as low as 15 months (range 10-23).[2, 20] Familial NB often presents younger at a median of 9 months of age.[21] The median age at diagnosis for LR disease in the SIOPEN trial was 11 months[22] and varied between 5.4 and 18 months according to stage for IR in COG studies.[23, 24] In two North American studies, Kreismann et al and Park et al, respectively, concluded that the median age at diagnosis for patients with HR disease were 37.0 months (range 2.4-349.2) and 37.2 months (range 23.0-53.6).[25, 26] The SIOPEN HR trial had a median age of 36 months (range 26.4-52.8).[27] An Indian review, representative of LMIC, reported median age at diagnosis between 30 and 42 months for NB,[28] while a Chinese study reported median age at diagnosis of 42 months.[29] The total South African cohort had a median age at diagnosis of 31 months comparable to LMICs. When the South African median age at diagnosis for LR (11 months), IR (16 months), and HR (36 months) are individually evaluated, the median ages at diagnosis per risk group were comparable to HICs. In North America, up to 36% of patients with NB were diagnosed before the age of 2 years,

while 90% were diagnosed by 5 years.[2] In this South African cohort, we found that 38.9% was diagnosed before 2 years, while only 80.1% of the cohort was diagnosed by 5 years, and the remaining 19.9% was diagnosed after 5 years, which differ from HICs (see Figure 1).[1]

A possible explanation for older median age at diagnosis in the South African study is that a greater percentage of the cohort (77% in South Africa vs <70% in HIC)[30] comprised of HR patients older than 18 months. HICs have superior diagnostic capacities to diagnose children at a younger age, which included the NB infant screening studies in Japan and Germany.[30, 31] A German study concluded that there was a substantial overdiagnosis of nonmetastatic NB estimated at a rate of 7/100 000 children (95% CI, 4.6-9.2), while screening did not identify more metastatic NB.[31] Similarly, Japanese studies screening only benefited the younger age groups, including those tumors that would otherwise have spontaneously regressed.[30] Therefore, the median age at diagnosis for the entire South African cohort was predominantly determined by the HR cohort with a higher median age at diagnosis.

In the COG study, a range of significant ages at diagnosis between 12.2 and 20 months were reported to be potential cut-point values.[2] The same was true for the total and HR cohort in the South African study (Table 3). When determining a potential cut-point value, or binary value, we prioritized a higher sensitivity. The range between 12.2 and 20 months in the North American study[2] would include the South African 19.1-month potential cut-point value for the total cohort. The HR cohort represented 77.0% of the South African cohort and had an optimal cut-point value of 18.4 months. In the South African cohorts, both the 18.4- and 19.1-month cut-point values were significant predicting OS according to the Kaplan-Meier curves. In the North American study, even adjusted for stage and MYCN status, it was found that the optimal adjusted age cut-off for a decreased risk of an event was at 19.7 months.[2]

Although the INRG risk classification incorporates the 18-month international age cut point, the stratification was developed from an overall cohort.[2] Therefore, the South African HR cohort was not compared to the 18-month international age cut point. Although the total cohort from the South African study was evaluated in terms of the total cohort of the North American study, the South African study defined OS as the end point and the North American study event-free survival.[2] The South African OS is poor compared to HICs mostly due to high incidences of advanced disease at diagnosis and limited access to autologous stem cell transplantation, *cis*-retinoic acid, and no access to immune therapy. The effect of the difference in OS on the age cut-point values was not evaluated.

5 LIMITATIONS

Data collection was retrospective and treatments in the various POUs were not standardized. The first international studies to determine an optimal cut-point value for the age of diagnosis predates the 2000s. Our own cohort includes patients between 2000 and 2016. During these periods, the diagnostic strategies have changed and may possibly affect the South African age estimates and comparisons. We acknowledge the relative bias in determining optimal cut-point values innate to the analysis of ROC curves. In the determination of cut-point values, the data were not adjusted for other prognostic factors such as stage and biological features. The INRG criteria were used for risk stratification and depend on a predetermined age cut-point value. This possibly affected the analysis of the age cut point in the HR group.

6 CONCLUSION

Age is one of the most important prognostic factors in the management of NB. This South African cohort for the age at diagnosis had a wide range of cut-point values up to 25 months, with the possibility of prognostic significance for OS. The 18-month cut-point value appears to be the appropriate age for prognostic determination despite the higher median age at diagnosis in South Africa.

ACKNOWLEDGMENTS

Jaques van Heerden, as staff member of the Department of Paediatric Haematology and Oncology, Antwerp University Hospital, University of Antwerp, acknowledges the Department for research support. The authors acknowledge the SACCSG for supporting the study, and the South African Children's Tumour Registry (SACTR) for providing statistical data. Permissions to reproduce the figure from London et al and the INRG classification system from Cohn et al were obtained from The Journal of Clinical Oncology for academic and manuscript purposes in July 2020.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTORS

Jaques van Heerden conceptualized and designed the study, collected the data, performed the data analysis, and wrote the manuscript. Mariana Kruger assisted with concept development, as well as design of the study, supervised data analysis, and critically reviewed and revised the manuscript. Tonya Esterhuizen performed the statistical analysis. The remaining authors collected the data in their respective pediatric oncology units and contributed significantly to the manuscript.

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