SA Journal of Oncology
ISSN: (Online) 2523-0646, (Print) 2518-8704

Neuroblastoma survival in South African children is more influenced by biological than socioeconomic factors

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Dates:
Received: 03 Aug. 2022
Accepted: 26 Oct. 2022
Published: 12 Dec. 2022

How to cite this article:
Charlton R, Ngcanad T, Geel J. Neuroblastoma survival in South African children is more influenced by biological than socioeconomic factors. S. Afr. j. oncol. 2022;6(0), a244. https://doi.org/10.4102/sajo.v6i0.244

Background: Optimal management of neuroblastoma depends on accurate risk stratification at diagnosis. Many low- and middle-income countries lack access to specific genetic tests used globally for this purpose.

Aim: To determine whether socioeconomic factors predict prognosis in neuroblastoma and could therefore provide alternative measures for risk stratification in resource-constrained settings.

Setting: The three main paediatric oncology units in Johannesburg, South Africa: Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and Wits Donald Gordon Medical Centre.

Methods: This retrospective record review included 145 patients presenting with biopsy-proven neuroblastoma between 01 January 2000 and 31 December 2018. Kaplan–Meier survival analysis was performed in relation to biological and socioeconomic factors, the latter including parental employment status, nationality, and distance of residence from treating facility. Cox proportional hazards regression analysis assessed the significance and effect of these prognostic factors.

Results: Factors with significant effect on survival were age below 18 months ($p < 0.0001$), extra-abdominal primary tumour site ($p = 0.02$), lower stage ($p < 0.001$), serum ferritin level< 0.0001) and favourable International Neuroblastoma Pathological Committee histology ($p < 0.0001$), race ($p = 0.005$), nationality ($p = 0.05$) and paternal employment ($p = 0.02$). The association between distance from treating facility and stage at diagnosis was not significant ($T_b = 0.108$, $p = 0.06$).

Conclusion: Biological factors exert a great influence on neuroblastoma survival than the socioeconomic factors analysed. This suggests that tumour biology exerts an overriding influence on prognosis in neuroblastoma.

Keywords: neuroblastoma; prognosis; survival; socioeconomic factors; distance.

Introduction

Neuroblastoma is a childhood malignancy with a highly variable clinical course. Outcomes range from spontaneous regression in some infants to highly aggressive disease in many older children, with survival rates of greater than 90% in low-risk groups and less than 50% in high-risk groups.[1] Risk stratification is based on distinct clinical, biological and genetic factors, which have been shown to influence prognosis.[2] Important clinical and biological factors include age, stage at diagnosis, tumour histology and levels of non-specific tumour markers such as ferritin and lactate dehydrogenase (LDH).[2,3] Genetic factors include MYCN gene amplification status, DNA index and specific genetic abnormalities such as chromosome 17q gain, 1p36 deletion, 11q aberration and 1p, 3p or 14q loss.[4]

These factors have been well-described and are frequently used for risk stratification in high-income countries (HIC).[5] In the United States, both the Children's Oncology Group (COG) and the International Neuroblastoma Risk Group (INRG) recommend using DNA ploidy in determining risk while the INRG also places importance on the presence of chromosome 11q aberration.[5,6] These genetic tests are currently inconsistently available in the public sector of low- and middle-income countries (LMICs) such as South Africa, where resource limitations are a constant challenge in the

healthcare system. If privately or self-funded, MYCN amplification and chromosome 11q deletion testing in South Africa will cost a patient R6016.60 ($375.00) (Ampath Laboratories). The national minimum wage as of March 2021 is R21.69 ($1.35)/hour which equates to less than R4000.00 ($250.00)/month.[7] A 2016 National Treasury report stated that 51.1% (6.7 million) of working South Africans earned less than R4000.00 ($250.00) a month,[8] while the World Bank data for 2020 shows that the formal unemployment rate in South Africa was as high as 32.5%.[9] These tests would therefore be unaffordable for the vast majority of South Africans.

It is thus important to identify additional low-cost prognostic factors that could be used for neuroblastoma risk stratification in resource-limited settings. Such factors would not replace any of the established clinical and biological prognostic factors, as these are indubitably strong predictors of prognosis in this highly biologically driven disease, but rather supplement available factors in situations where the more expensive of the biological factors are not available. Higher socioeconomic status has been shown to correlate with higher survival rates for certain paediatric cancers in all income settings.[10,11] No studies in Africa have yet looked specifically at socioeconomic determinants of survival in neuroblastoma. We explored the possibility that socioeconomic factors might influence survival in neuroblastoma in the LMIC of South Africa. This would allow for identification of low-cost prognostic factors that could be used to supplement neuroblastoma risk stratification in the resource-limited settings of many LMICs.

Methods

Setting

This multicentre retrospective record review was conducted at the three main paediatric oncology units (POUs) in Johannesburg, South Africa, all affiliated with the University of the Witwatersrand.

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) serve the public sector, offering specialist services primarily to the communities of Johannesburg and Soweto. Together they offer approximately 4300 beds and serve a population of greater than 3 million, with referrals from sub-Saharan Africa.[12,13] These are the only two facilities offering paediatric oncology services to the public sector of Johannesburg. Wits Donald Gordon Medical Centre (WDGMC), on the other hand, is a 140-bed facility serving the private sector of Johannesburg. It offers specialist and sub-specialist services to patients who can afford privately funded medical care.[3,4] These three centres serve the primarily urbanised population of Johannesburg, the most densely populated city in Gauteng province (2900 people/km^2), itself the most densely populated province within South Africa (809.6 people/km^2). Other resources for paediatric cancer care that are available in Johannesburg include non-profit organisations, which provide additional financial and psychosocial support to families and caregivers of children with cancer.

Study population

The study population included all pathologically confirmed (on tumour histology of excision specimens, fine needle aspirate or trephine biopsy), previously untreated cases of neuroblastoma in patients under the age of 18 years who presented to any of the three main POUs in Johannesburg between 01 January 2000 and 31 December 2018. Exclusion criteria included patients for whom records were substantially incomplete and those who declined treatment. Patients were identified from the POU databases at each hospital.

Data collection

The endpoint of the study was defined as 2-year overall survival (OS). The clinical and biological prognostic factors studied included age less than or greater than 18 months, stage at diagnosis as defined by the International Neuroblastoma Staging System (INSS), site of primary tumour, non-specific tumour markers (ferritin levels of less than or greater than 120 µg/L, LDH levels of less than or greater than 750 U/L, as per the SIOP-PODC adapted risk stratification and treatment guidelines),[2] MYCN amplification status (no change, gain or amplification) and International Neuroblastoma Pathological Committee (INPC) classification (favourable or unfavourable).[5] International Neuroblastoma Staging System staging was used as this was the predominant staging system in South Africa for the majority of the study period.

Socioeconomic factors included nationality (South African or non-South African), self-identified race (black or white), maternal and paternal employment status (employed or unemployed), distance of residence from treating facility (in kilometers, using the Google Maps® distance calculator) and parental income, using the proxy of hospital financial classification (see Supplementary Table 1). Hospital financial classification in the public sector of South Africa is principally determined based on combined household income. Where the exact address was not available for patients from other countries, the capital of that country was used as a reference for distance. Employment status of each parent was obtained from the initial medical history notes. In cases where the father was not involved in the patient's life and not contributing financially, paternal employment status was recorded as 'unemployed'. Races other than black and white were not included in the analysis owing to their comparatively small numbers.

Statistical analysis

Data captured in the REDCap® database were exported to Excel for descriptive analysis and to Medcalc Statistical Software® for survival analysis. Descriptive statistics were presented as frequencies and percentages for categorical data. Continuous variables were presented as the mean

TABLE 1: Survival analysis of clinical, biologic and socioeconomic factors in South African neuroblastoma patients.

Characteristic	Frequency		2-Year OS (%)	HR	95% CI	Significance (*p*)
	n	%				
Gender						0.98
Male	75	51.7	39.4	1.00	0.65–1.51	
Female	70	48.3	35.7	1.01	0.66–1.53	
Age						< 0.0001
< 18 months	53	36.6	59.0	2.62	1.71–4.02	
> 18 months	92	63.4	26.2	0.38	0.25–0.58	
Race						0.0005
White people	29	20.0	65.3	2.31	1.44–3.72	
Black people	110	75.9	29.7	0.43	0.27–0.69	
Asian/mixed race people	6	4.1	-	-	-	
Nationality						0.05
South African	129	89.0	40.9	2.11	1.01–4.38	
Non-South African	16	11.0	18.8	0.48	0.23–0.99	
Hospital classification						0.06
Privately paying	61	42.1	47.5	1.49	0.98–2.28	
State-subsidised	84	57.9	31.7	0.67	0.44–1.02	
Maternal employment						0.26
Employed	60	41.4	41.5	1.29	0.82–2.02	
Unemployed	65	45.5	31.2	0.77	0.49–1.21	
Undocumented	20	13.8	-	-	-	
Paternal employment						0.02
Employed	92	63.4	44.3	1.96	1.11–3.48	
Unemployed	30	20.7	26.7	0.51	0.29–0.90	
Undocumented	23	15.9	-	-	-	
Stage						< 0.0001
1	6	4.1	100.0	5.20	-	
2	10	6.9	88.9	-	3.37–8.02	
3	31	21.4	74.2	-	-	
4	93	64.1	16.1	0.19	0.12–0.30	
4S	5	3.4	60.0	-	-	
Primary tumour site						0.02
Extra-abdominal	36	24.8	55.4	1.75	1.10–2.80	
Abdominal	105	72.4	34.0	0.57	0.36–0.91	
Undocumented	4	2.8	-	-	-	
Ferritin						0.003
< 120 µg/L	65	44.8	52.1	1.97	1.26–3.08	
> 120 µg/L	67	46.2	29.4	0.51	0.32–0.78	
Undocumented	13	9.0	-	-	-	
LDH						< 0.0001
< 750 U/L	49	33.8	67.1	3.24	2.08–5.04	
> 750 U/L	87	60.0	24.0	0.31	0.20–0.48	
Undocumented	9	6.2	-	-	-	
MYCN status						
No change	34	23.4	-	1.60	0.93–2.73	0.09
Gain	22	15.2	53.1	-	-	
Amplified	43	29.7	32.4	0.63	0.37–1.07	
Undocumented	46	31.7	-	-	-	
INPC classification						< 0.0001
Favourable	23	15.9	95.7	4.54	2.45–8.39	
Unfavourable	63	43.4	34.2	0.22	0.12–0.41	
Undocumented	59	40.1	-	-	-	

OS, overall survival; LDH, lactate dehydrogenase; INPC, International Neuroblastoma Pathological Committee; HR, hazard ratio.

with standard deviation for normally distributed data or median with interquartile range (IQR) for non-normally distributed data.

Overall survival was defined from the date of diagnosis until the date of death or date last seen. Survival analysis was performed using Kaplan–Meier curves. Univariate analysis was performed using Cox proportional hazards regression to determine the statistical significance and size of effect for each of the prognostic factors under study. A *p*-value of less than 0.05 was considered statistically significant. The complete data sets numbered 48, which was too few to

perform multivariate analysis or accurate correlation tests between variables. A Kendall's tau-b correlation was calculated to determine the relationship between distance of residence from treating facility and stage at diagnosis, both for South African patients only and with inclusion of international patients.

Ethical considerations

The Human Research Ethics Committee (Medical) of the University of the Witwatersrand granted unconditional approval for the study (approval number M200311).

Results

Patient characteristics

During the study period, 164 patients with neuroblastoma were identified. Of these, 19 were excluded: 16 because the files were missing, one because the patient had received prior treatment and two because the family declined treatment based on cultural beliefs about alternative curative treatment methods for advanced disease. This resulted in a total of 145 patients (Figure 1).

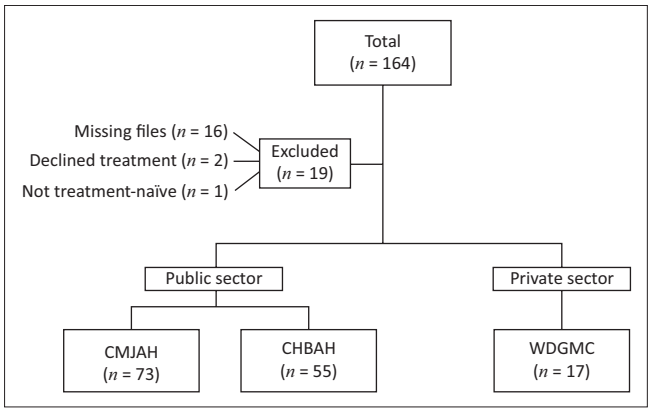
The demographic and socioeconomic data as well as disease characteristics of the study population are presented in Table 1.

The male to female ratio was close to equal (gender ratio = 1.07:1). The median age of presentation was 2.3 years (IQR: 0.9–4.2 years). There were 110 (75.9%) black patients, 29 (20%) white patients, four (2.8%) Indian/Asian patients and two (1.4%) mixed-race patients. The latter two groups were excluded from analysis involving race. The site of primary tumour was the adrenal gland in 86 (59.3%) cases, thorax in 23 (15.9%), other abdominal in 19 (13.1%), cervical region in eight (5.5%), pelvis in three (2.1%) and subcutaneous tissue in two (1.4%). The primary site was undocumented in four cases (2.8%), all because of late presentation with widespread disseminated disease and inability to accurately locate the primary tumour. International Neuroblastoma Pathological Committee classification was undocumented in 40.7% because of lack of tissue submission before treatment, where a diagnosis was made on bone marrow trephine or fine needle aspirate alone.

The median distance of residence from treating facility was 31.4 km (IQR: 15 km – 169 km, absolute range: 2.5 km – 7231 km). All patients who lived greater than 1000 km from the treating facility were from other sub-Saharan African countries. The nationality of 89% of patients was South African. Patients were distributed across eight separate hospital classifications based on age and parental income (Supplementary Table 1).

Survival analysis

The 2-year OS rate for the entire study population was 35.9%. Demographic factors with higher 2-year OS rates included age less than 18 months (59% vs 26.2%, $p < 0.0001$). White patients had a 2-year OS of 65.3% and black patients 29.7% ($p = 0.0005$). South African patients had higher survival rates (40.9%) than their non-South African counterparts (18.8%, $p = 0.05$). Gender was not significant in predicting prognosis ($p = 0.98$).



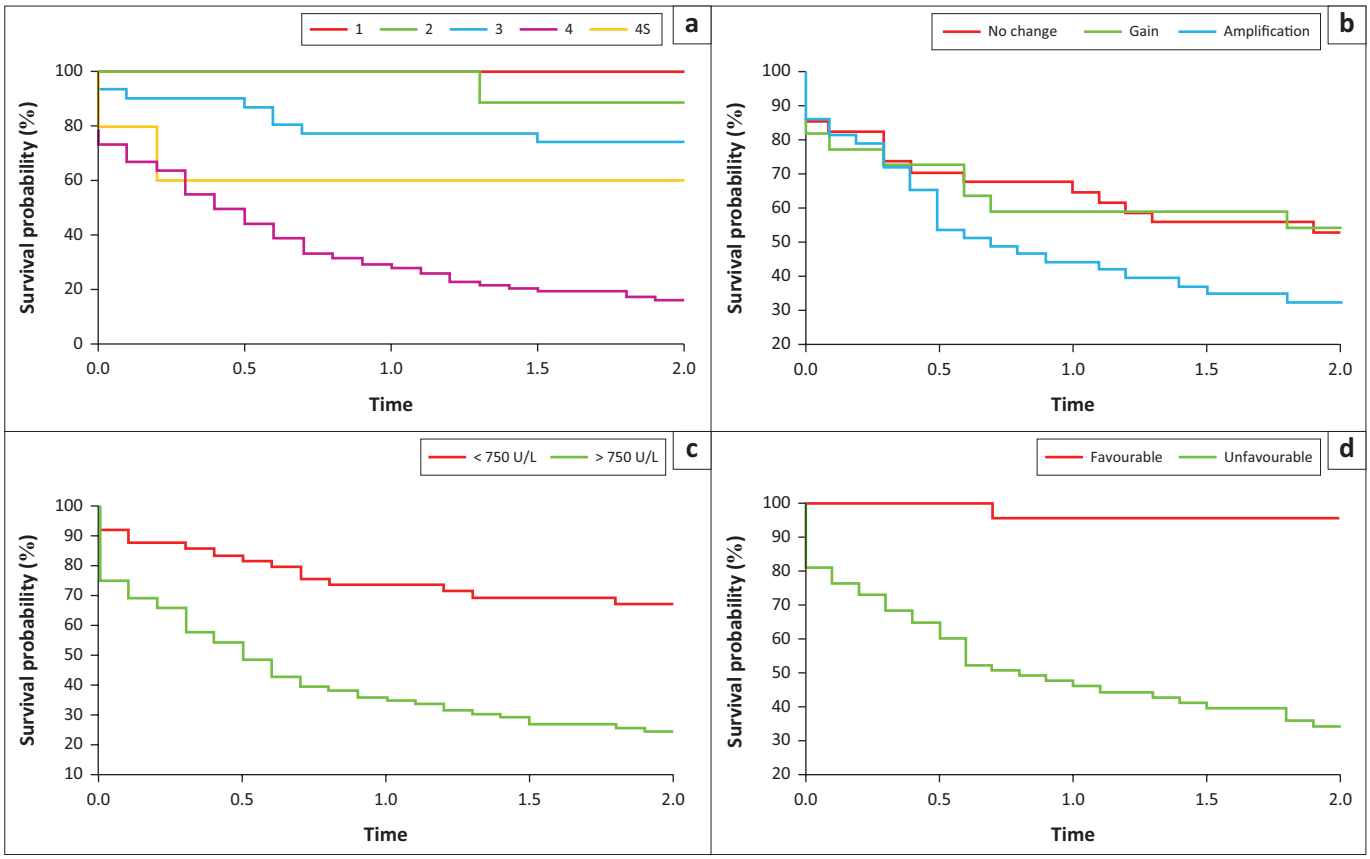
CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; CHBAH, Chris Hani Baragwanath Academic Hospital; WDGMC, Wits Donald Gordon Medical Centre.

FIGURE 1: Consort diagram showing the selection of study participants.

TABLE 2: Survival analysis according to distance of residence from treating facility in South African patients with neuroblastoma.

Distance of residence from treating facility	Frequency		2-Year OS (%)	HR	95% CI	Statistical significance (p)
	n	%				
20 km						0.12
< 20 km	52	40.3	45.7	1.43	0.91–2.26	
> 20 km	77	59.7	37.0	0.70	0.44–1.10	
30 km						0.21
< 30 km	69	53.5	43.0	1.34	0.85–2.10	
> 30 km	60	46.5	37.8	0.75	0.48–1.18	
40 km						0.22
< 40 km	86	66.7	42.6	1.35	0.83–2.18	
> 40 km	43	33.3	36.4	0.74	0.46–1.20	
50 km						0.10
< 50 km	94	72.9	44.3	1.54	0.92–2.56	
> 50 km	35	27.1	31.2	0.65	0.39–1.09	
100 km						0.18
< 100 km	106	82.2	42.6	1.49	0.83–2.70	
> 100 km	23	17.8	31.5	0.67	0.37–1.21	

OS, overall survival; HR, hazard ratio.



LDH, lactate dehydrogenase; INPC, International Neuroblastoma Pathological Committee.

FIGURE 2: Kaplan–Meier survival curves of biological risk factors for children with neuroblastoma. (a) Stage at diagnosis, (b) MYCN amplification, (c) LDH level and (d) INPC Histology calcification.

Patients with stage 1 disease had 100% survival at two years while those with stage 4 disease had a 2-year OS of 16.1%. There was a higher 2-year OS in patients with an extra-abdominal site of primary tumour (55.4% vs 34%, $p = 0.02$), lower levels of serum ferritin (52.1% vs 29.4%, $p = 0.003$) and serum LDH < 750 U/L (67.1% vs 24%, $p < 0.0001$), and a favourable INPC classification (95.7% vs 34.2%, $p < 0.0001$). Kaplan–Meier survival curves in relation to some of these biological factors are demonstrated in Figure 2.

On Cox proportional regression analysis, factors with a significant effect on survival were age less than 18 months (hazard ratio [HR]: 2.62 [95% CI], $p < 0.0001$), stage lower than stage 4 (HR: 5.20 [95% CI], $p < 0.001$), extra-abdominal primary tumour site (HR: 1.75 [95% CI], $p = 0.02$), ferritin level < 120 µg/L (HR: 1.9685 [95% CI], $p = 0.003$), LDH level < 750 U/L (HR: 3.24 [95% CI], $p < 0.0001$) and favourable INPC classification (HR: 4.54 [95% CI], $p < 0.0001$). The MYCN amplification status did not have a significant effect on survival in our study (HR: 1.60 [95% CI], $p = 0.09$).

South African nationality ($p = 0.05$) and paternal employment ($p = 0.02$) were associated with higher survival while neither maternal employment status ($p = 0.26$) nor hospital classification ($p = 0.06$) were associated with higher survival (Figure 3).

A weakly positive but insignificant correlation was found between distance of residence from treating facility and stage at diagnosis, both international patients were included ($T_b = 0.11$, $p = 0.06$, 95% CI: 0.09–0.22) and excluded ($T_b = 0.08$, $p = 0.19$, 95% CI: –0.07–0.19) (see Table 2) from analysis.

Discussion

To the best of the authors' knowledge, this study is the first in Africa to look specifically at the effect of socioeconomic factors on prognosis in neuroblastoma. It demonstrated that, in the South African setting, survival in neuroblastoma was affected by socioeconomic factors such as race, nationality and paternal employment status as well as almost all biological factors analysed. The differential in survival between white and black patients was stark and concerning.

The demographic profile of the patients in this study was in keeping with that of neuroblastoma patients seen globally, with an almost equal gender ratio and the majority of patients presenting below the age of five years. The median age in our study of 28 months was, however, higher than the 22 months reported globally[14] but in keeping with a previous study conducted in South Africa.[3] As older age is associated with a worse prognosis, this could help to explain the generally poor outcomes noted in our study, in which 64.1% of the patients presented with stage 4 disease.

The association between black race and a markedly lower survival rate cannot be ignored. A biological basis does not

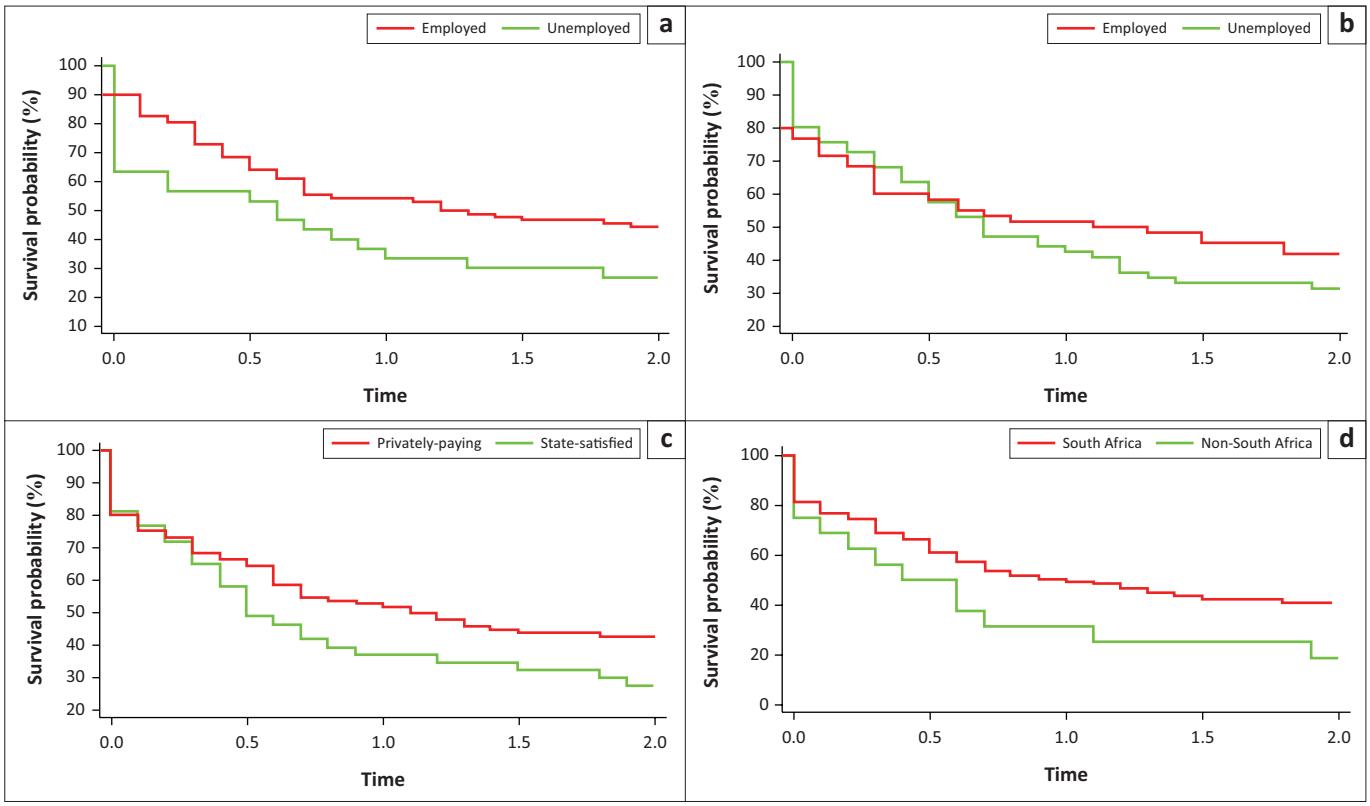


FIGURE 3: Kaplan–Meier survival curves of socioeconomic parameters for children with neuroblastoma. (a) Father employed, (b) mother employed, (c) hospital classification and (d) nationality.

explain this differential survival, and the social construct of race parallels closely with socioeconomic status.[15] Differences in neuroblastoma survival between racial groups are likely because of socioeconomic inequalities, especially the enforced historical impoverishment of black people in South Africa, rather than true biological differences. Significant income inequalities exist between racial groups in South Africa. In 2015, real income was lowest in black South Africans (R6899.00 ($435.00)/month), 1.4 times higher than mixed-race people (R9339.00 ($585.00)/month), 2.1 times higher in Indians/Asians (R14 235.00 ($887.00)/month) and 3.6 times higher in white South Africans (R24 646.00 ($1536.00)/month).[16] Lower income could correlate with reduced access to healthcare, and the possibility of institutional or systemic racism in the treating centres cannot be ignored.

Congruent with other studies,[11,17] a lower 2-year OS was associated with age older than 18 months at diagnosis, higher ferritin and LDH levels, unfavourable INPC classification and more advanced stage at presentation. The MYCN amplification status was not shown to have significant prognostic value. This difference from global observations that MYCN amplification is strongly associated with poor prognosis, so much so that its presence automatically makes a patient high risk regardless of age or stage.[2] It is possible that our findings differed because 37.1% of study participants had undocumented MYCN status owing to the poor availability of MYCN testing in South Africa during the early parts of the study period. This significantly reduced the number of patients who had analysable MYCN results (only 99 patients remaining in the sample), which could explain the lack of association between MYCN and neuroblastoma survival despite it being a well-established prognostic factor.

Of those biological factors shown to have a significant effect on survival, the factors with the strongest association were stage, INPC classification and LDH level. The likelihood of survival to two years was 5.2 times higher in those with stage other than stage 4, 4.5 times higher in those with a favourable INPC classification, 3.2 times higher in those with LDH levels < 750 U/L, 2.0 times higher in those with ferritin < 120 µg/L and 1.8 times higher in those with extra-abdominal primary tumour site.

Globally, paediatric cancer appears to be influenced to a greater or lesser degree by socioeconomic factors depending both on the type of cancer itself and the World Bank income classification of the country in which treatment is sought. For paediatric cancers as a whole, measures of low socioeconomic status appear to be consistently associated with poorer outcomes in LMIC, while the association is less consistent in HIC.[11,17]

Parental income is one such socioeconomic factor. In paediatric acute lymphoblastic leukaemia in India, parental income was shown to be inversely proportional to mortality with lower parental income being associated with greater mortality. Postulated explanations for this include 'resource burn out' as treatment progresses, eventually contributing to a lack of adherence and treatment abandonment in patients

from families with fewer financial resources.[10] The association of lower parental income with higher mortality was also found in other studies of paediatric cancers,[11] with one systematic review finding the association to be stronger in LMIC than HIC.[17] However, the number of studies conducted on this topic in LMIC is limited.

In our study, parental income (as investigated using hospital classification) was not significantly associated with neuroblastoma outcome. A possible explanation for the lack of association could be that hospital classification did not always accurately reflect parental income. According to the *National Health Act (no 61 of 2003)*, children under the age of six are entitled to free healthcare regardless of parental income unless they have private medical aid (PM) or are non-citizens (PF).[18] This classification was inconsistently assigned in the records analysed here; some South African patients under the age of six without medical insurance were correctly classified as H0/HG while others were given classifications of H1–H3 depending on household income. For every patient correctly classified as HG/H0, the exact income level of the parents was undocumented and so could have skewed the results.

Parental employment is another socioeconomic factor that has been postulated to influence paediatric cancer survival, although studies investigating this relationship in LMIC are lacking. A retrospective study conducted in high-income Finland found an association between maternal employment and cancer outcome, but only if adjustment was made for other socioeconomic factors.[11] When a family's socioeconomic situation was secure, maternal unemployment was found to be linked to lower childhood cancer mortality. This was postulated to be because of the ability of the unemployed but financially secure mother to dedicate a greater amount of time and resources to the sick child.[11] Our study did not detect a significant association between maternal employment status and survival in children with neuroblastoma.

While maternal employment did not affect neuroblastoma survival in our study, a positive correlation was found between paternal employment and survival (HR: 1.96 [95% CI], $p = 0.02$). This could be explained by gender pay inequalities in South Africa: in 2020 it was estimated that 62.1% of households were male-headed, with such households being approximately 40% wealthier than those headed by women.[19] These wealthier male-headed households may potentially have increased access to healthcare and so higher rates of paediatric neuroblastoma survival.

Distance of residence from treating facility is an important factor in health service accessibility. The greater the travel distance to the hospital the greater the financial strain placed on the family; out-of-pocket travel expenses are increased, and income is often reduced when the accompanying parent needs to take a leave of absence from work to allow for the greater travel times involved.[20] Psychological wellbeing is also affected through disrupted social and family routines.[21]

These effects are particularly relevant in Africa, and in South Africa in particular, with its large immigrant population.[22] Many African people have been displaced and forced to reside in poorly resourced settings because of sociopolitical disruptions resulting from institutions such as civil war or economic hardship. Furthermore, many countries in Africa have poor access to the resources required for comprehensive cancer care. Citizens of these countries, if able to travel to a country such as South Africa for treatment, still tend to have poorer outcomes than South African cancer patients. This could be because of the delay in treatment associated with arranging transport and travelling the large distances between their homes and the treating centre. In addition, these patients are far from their social support systems and limited in their ability to earn an income. Access to specialized healthcare is particularly difficult for non-citizens of a country who have entered the country either as refugees or as economic migrants, often without the necessary documentation. Challenges include both xenophobia in the host country and barriers to legal entry or resident status in the country.

Given these negative effects of greater travel distance on the patient and their family, it might be expected that survival would also be negatively affected by greater distance from the treating facility. Little research has been performed till date on the effect of travel distance on paediatric cancer survival, and none on neuroblastoma survival. In Australia, rurality is more important than actual travel distance in predicting outcome in paediatric cancer, with poorer survival in patients from more isolated and rural areas regardless of actual travel distance.[21] This finding is supported by a recent systematic review, which also found an association between rural status and poorer survival in paediatric cancer, while the association between actual travel distance and survival was less consistent.[23]

While there initially appeared to be a survival benefit to shorter distance between residence and POU, the supposed benefit remained similar regardless of the distance analysed (20 km, 30 km, 40 km, 50 km, 100 km) and was not significant when analysed without the inclusion of international participants (Table 2). While these international patients did have the greatest distance to travel between place of residence and treating facility, their survival was influenced by additional factors such as having the financial means to seek privately funded medical care in a different country. As distance did not appear to affect survival when only those patients from South Africa were looked at, it is likely that other factors play a greater role in predicting survival in these patients than distance of residence from treating facility. Although survival was unaffected by travel distance, our study found that more than two thirds of patients who presented with stage 4 disease lived greater than 20 km from the treating facility. A South

African adult breast cancer study found a significant relationship between greater distance from hospital and risk of late-stage diagnosis.[24] This association did not prove to be significant for stage of neuroblastoma and distance from treating facility in our study when analysed either with the inclusion of international patients ($T_b = 0.11, p = 0.06$) or without ($T_b = 0.08$, $p = 0.19$), but the limited sample size may have influenced this finding.

Limitations of the study include missing data such as the undocumented MYCN amplification status in as many as 31.7% of study participants. The choice of proxies for socioeconomic status could also have influenced the results of this study; parental income may not be adequately represented by hospital classification, thereby explaining the lack of association in our study despite an association being found in other LMIC. The postsurgical INSS staging system has largely been superseded by staging systems based on pre-treatment image defined risk factors. Limitations of the INSS staging system include a lack of uniformity and a poor ability to stage tumours managed without surgical intervention.[25]

Survival is affected by a complex interaction between multiple factors. This is particularly true in LMIC where the social determinants of health influence health inequities. Future studies may address reasons for survival differences between patients of different races and socioeconomic groups and the effects of increased income and psychosocial support on vulnerable patient groups.

Conclusion

Neuroblastoma, especially stage 4 disease, is a highly aggressive malignancy and is strongly driven by biological factors such as genetic and chromosomal alterations in the tumour. This study demonstrated that socioeconomic factors play a limited role in predicting outcome in this disease. It may therefore be that the very nature of late-stage neuroblastoma has an overriding influence on survival, which is not offset by external, socioeconomic factors.

Acknowledgements

The authors would like to thank Prof. Ziyaad Dangor for his review of the manuscript. They would also like to thank Prof. Elena Libhaber and Dr Zvifadzo Matsena-Zingoni for their invaluable assistance with the statistical analysis.

This article abstract was presented at the 54th Annual Congress of the International Society of Paediatric Oncology (SIOP), 21–24 October 2021. Socioeconomic factors and distance from treating centre do not predict survival in South African children with neuroblastoma. (https://2021.siop-congress.org/ (poster presentation) and the 14th SIOP Africa Continental Congress. March 16–18 2022. Socioeconomic factors and distance from treating centre do not predict survival in South African children with neuroblastoma. (https://siopafrica.org/ (oral presentation).

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

R.C. and J.G. contributed to the design and implementation of the research, analysis of results and to the writing of the article. T.N. assisted in the collection of data and review of the article.

Funding information

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data availability

The data that support the findings of this study are available on request from the corresponding author, R.C. The data are not publicly available because of their content that could compromise the privacy of research participants.

Disclaimer

All views expressed in this article are the authors' own and not an official position of the University of the Witwatersrand or any of the hospitals included in this study.

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