Retinoblastoma in Tanzania; Survival and prognostic factors: A retrospective cohort study

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ABSTRACT

Objective: To determine the 3-year survival rate and prognostic factors among patients with retinoblastoma diagnosed at Muhimbili National Hospital from January 2016 to December 2018.

Methods: A retrospective cohort study was conducted. Participants were consecutively recruited. Data were collected using a questionnaire. Variables included demographics, clinical presentation, treatment, and survival time. Statistical analysis was performed using Stata version11. Kaplan-Meier survival analysis was used to assess the survival rates, while the log rank test determined statistical significance. The hazard ratios were calculated using Cox regression. A P value < 0.005 was considered statistically significant.

Results: A total of 166 children were studied, with 69.3% having unilateral retinoblastoma and 30.7% bilateral. Fifty percent of the children were females. The overall mean age at diagnosis was 25.56 ± 15.56 months. The participant's mean age at diagnosis was 18.7± 11.6 months for bilateral and 31.3± 20.4 months for unilateral retinoblastoma. The most common complaints were leukocoria (90.4%) and eye protrusion (46.4%). The mean duration of symptoms was 7.9±5.3 months, and the mean total delay time was 9.4±5.6 months. At presentation, 51.8% of the study participants had disease stage 3 and 4 according to the International Retinoblastoma Staging System. The 3-year Kaplan-Meier survival rate was 52.3%. Multivariate Cox regression analysis identified age at diagnosis > 24 months (p=0.001), failure to complete treatment (p=<0.001), and extra-ocular disease invasion (p=0.008) as factors associated with lower survival rates.

Conclusion: The 3-year survival rate of patients with retinoblastoma in our setting was 52.3%. Age at diagnosis of >24 months, failure to complete treatment, and extraocular disease invasion were associated with a lower survival rate.

Key words: Survival rate, Retinoblastoma, Late presentation, Leukocoria

INTRODUCTION

Retinoblastoma (Rb) is the most common intraocular malignancy in young children, with an estimated incidence of 1 in 20,000 births worldwide (ranging from 1 in 14,000 to 1 in 34,000)[1, 2]. In high-income countries, Rb is curable, and deaths from this cancer are rare[3]. In Africa, however, Rb is the most prevalent life-threatening ocular cancer in children under five, associated with a higher mortality rate[4, 5]. Rb is a potentially curable disease with very high disease-free survival if early detected and managed appropriately[1,2]. However, late diagnosis and treatment result in significantly higher mortality and morbidity, leaving some survivors completely blind with severe emotional difficulties and limited participation in educational, economic, and social activities[6].

The survival rates for retinoblastoma vary significantly worldwide. The 3-year survival rate is 99.5% in high-income countries, 91.2% in upper-middle-income countries, 80.3% in lower-middle-income countries, and 57.3% in low-income countries[7]. Lower survival rates in developing countries, particularly in sub-Saharan Africa, are attributed to delays in seeking medical care, late diagnosis and treatment[9, 10]. Despite developing countries bearing greater (80–90%) of the disease burden, few studies have focused on retinoblastoma survival rates[6–8]. In spite of having a significant number of patients receiving treatment annually in our centre, the survival rate and prognostic factors remains unknown. Knowing the survival rates and prognostic factors may help in evidence based counselling to the parents and caretakers about Rb treatment. This can positively impact the decision of parents in accepting treatment without any delays and further increases the chances of survival. This study aimed at investigating the 3-year survival rate and associated prognostic factors among patients diagnosed with retinoblastoma at our centre from January 2016 to December 2018.

MATERIALS AND METHODS

Study design and study period: This was a retrospective cohort study conducted for a period of six months between June and December 2021.

Study setting: This study was conducted at Muhimbili National Hospital (MNH) which houses eye paediatric and paediatric oncology units providing both outpatient and inpatient services. The paediatric oncology and eye unit collaborates in a specialized programme dedicated for managing retinoblastoma patients. The two units are equipped for the diagnosis and management of early and late cases of retinoblastoma. An average of 60–80 cases of retinoblastoma are seen each year at MNH.

Study population: The study population included all patients with retinoblastoma diagnosed at MNH from January 1st, 2016 to December 31st, 2018.

Inclusion criteria: This study included all patients with a histologically confirmed diagnosis of retinoblastoma with complete 3 years follow-up time.

Exclusion criteria: All patients whose outcomes were unknown due to loss to follow-up and incomplete data.

Data collection procedure: Data was collected using a structured questionnaire. The principal investigator gathered information from the retinoblastoma data base and patients' files. This included demographic information, presenting complaints, duration of the symptoms, family history of retinoblastoma, disease laterality, disease stage according to the International Retinoblastoma Staging System (IRSS), types of treatment, time lag before treatment, and total delay time. It also collected information regarding the follow-up time and the survival status (alive or dead). Symptom duration was defined as the time from symptom onset, as noted by the parents or caretaker, to the first presentation at MNH. Total delay time was defined as the interval from the first time the parent noted the first symptom to the initiation of the first treatment at MNH.

Data analysis: Stata version 11.0 was used for data analysis. Kaplan-Meier survival analysis was performed to assess the survival rates, and statistical significance was tested by the log-rank test. Univariable and multivariable Cox regression were used to calculate unadjusted and adjusted hazards ratios. A p-value of <0.05 was considered statistically significant. The measure of outcome was survival. The survival time was measured from the date of diagnosis up to the 3-year follow-up time, or the time when death occurred.

Ethical consideration: Ethical clearance for the study was obtained from the Institutional Review Board of Muhimbili University of Health and Allied Science. Verbal consents were obtained from parents / caretakers through mobile phone calls. Participants had no risk in participating in this study and they were not paid anything. The study provided no direct benefit to the study participants but findings of the study if implemented can improve the survival rate in these patients.

RESULTS

Of the 184 patients diagnosed with retinoblastoma (Rb) from 2016 to 2018, 18 were excluded from the analysis due to loss to follow-up (15 patients) and incomplete data (3 patients). Of the 166 study participants included in the analysis, slightly more than half (51%) were females. The majority (99; 60%) of the participants were aged 2–24 months, 58 (34.9%) were aged 25–48 months, and nine (5.4%) were older than 48 months. The overall mean age at diagnosis was 25.56 months (± 15.56 months). The mean age at diagnosis was 18.7 (± 11.6) months for participants with bilateral retinoblastoma and 31.3 (± 20.4) months for those with unilateral retinoblastoma.

Table 1: Clinical characteristics and disease stage of the study participants at presentation

Characteristic	Frequency	
	No.	(%)
Laterality		
Unilateral	115	69.3
Bilateral	51	30.7
Presenting complaints		
Leukocoria	150	90.4
Eye protrusion	77	46.4
Eye redness/pain	46	27.7
Squint	16	9.6
Other symptoms	23	13.8
Recurrent tumour post enucleation	4	2.4

Family history of retinoblastoma	5	3.0
Duration of symptoms(months)		
< 3	30	18.1
3-6	54	32.5
>6	82	49.4
International Retinoblastoma Staging System (IRSS)		
Stage 1	40	24.1
Stage 11	40	24.1
Stage 111	48	28.9
Stage IV	38	22.9

Other symptoms included poor vision (12), nystagmus (4), headache (1), eye discharge (2), and vomiting (4).

Most (69.3%) participants had a unilateral disease. The most common (90.4%) presenting complaint was leukocoria. Nearly half (49.4%) of study participants had a duration of symptoms greater than 6 months. More than half (86; 51.8%) of the participants presented with advanced disease (stage 3 or 4) (Table 1).

The mean duration of symptoms was 7.9±5.3 months. The majority (122; 73.5%) of the study participants had a total delay time of ≥ 6 months, while only (44; 26.5%) had a total delay time of < 6 months from the onset of symptoms to treatment initiation. The mean total delay time from recognition of symptoms to treatment initiation was 9.4±5.6 months. In most (156; 94%) of study participants, the treatment was initiated within one month after diagnosis. About (7; 4.2%) of participants died in the course of treatment.

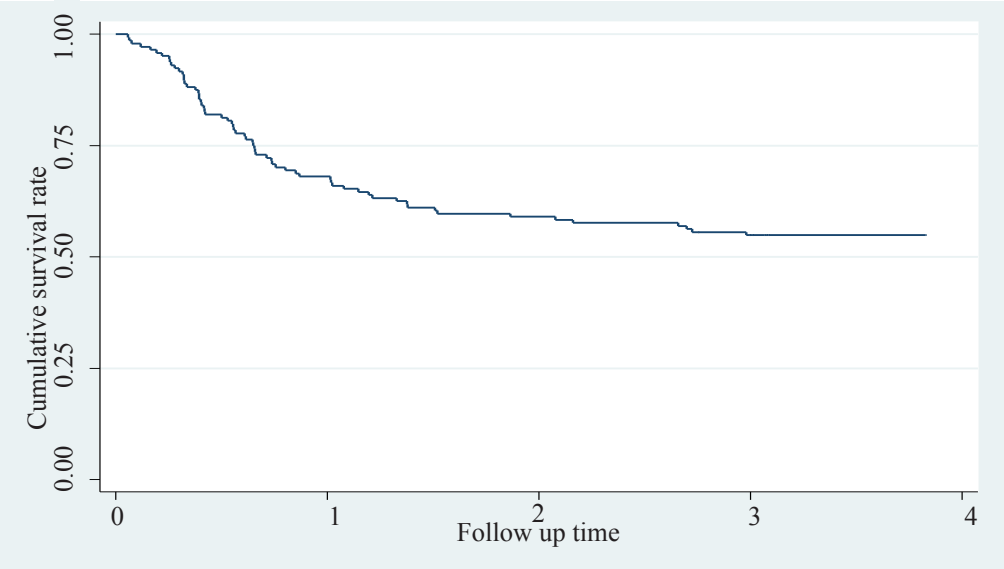
Table 2: Modality of treatments given to the study participants (n=166)

Variable	Frequency	
	No.	(%)
Modality of treatment given		
Primary enucleation alone	33	19.8
Primary enucleation with adjuvant chemotherapy	41	24.7
Primary enucleation with adjuvant chemotherapy and radiotherapy	06	3.6
Secondary enucleation with adjuvant chemotherapy	30	18.1
Secondary enucleation with adjuvant chemotherapy and radiotherapy	20	12.1
Palliative treatment	36	21.7

Many patients received more than one treatment modality. The patients who received chemotherapy without radiotherapy included those whose histology ruled out high-risk features. Three patients who were under the age of one year and eligible for radiotherapy did not receive it due to their young age. Twenty patients did not complete the required treatment.

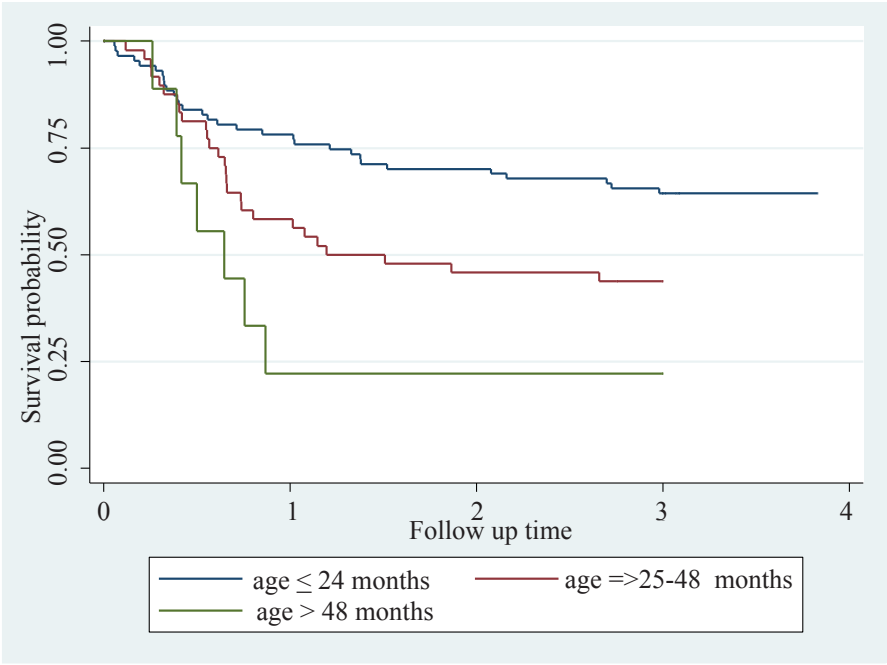
Survival rate analysis: The overall cumulative survival rate of the patients with retinoblastoma was 69%, 59.6% and 52.3% at 1, 2 and 3 years respectively (n=166) (Figure 1).

Figure 1: Kaplan -Meir survival rate for retinoblastoma patients



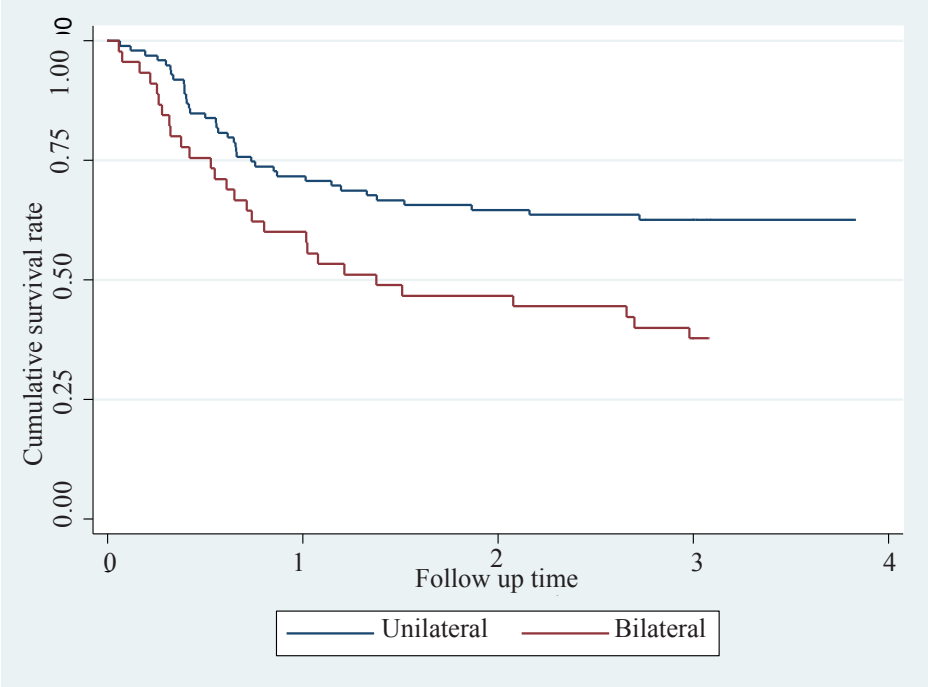
The 3- year survival rate was 99 (66%) for the participants diagnosed within the first 24 months of life. The survival rate for participants aged 25-48 months was 58 (44%) and 9 (22.2%) for participants aged 49 months and above. The survival rate difference between these age groups was statistically significant (log rank p= 0.0026). (Figure 2).

Figure 2: Kaplan-Meir survival rate of the study participants by age at diagnosis



The 3-year survival rate for participants with unilateral Rb was 115 (64.4%), while for bilateral Rb it was 51 (37.2%). The difference in survival rate between the two groups was statistically significant (log rank p = 0.0053) (Figure 3).

Figure 3: Kaplan-Meir survival rate of the study participants by disease laterality



The study participants with shorter duration of less than 3 months had a 3-year cumulative survival rate of 30 (86.6%), whereas those who presented after 3 months duration had cumulative survival rate of 54 (68.5%) and 82 (36.6%) for patients with symptoms lasting 3-6 months and >6 months respectively. There was a significant difference in survival rate between the groups (log rank p=0.0002).

Participants with time interval of less than six months from the first appearance of first symptom to the initiation of treatment had cumulative survival rate of 44 (86.4%) and those with time interval of greater than six months the survival rate was 122 (45.1%). There was a significant difference in survival rate between the two groups (log rank p=0.0004).

According to disease stage at diagnosis, participants with stage 1 disease had a survival rate of 40 (90%), stage 2 had a survival rate of 40 (77%), stage 3 had a survival rate of 48 (49.5%) and stage 4 had a survival rate of 38 (2.6%). The survival rate difference across the disease stages was statistically significant (log rank p= <0.0001).

Majority 130 (78.3%) of patients came with advanced disease which necessitated enucleation. Participants who underwent primary enucleation had higher survival rate (80; 80%) compared to those who underwent secondary enucleation (50; 58%). The difference in survival rate was statistically significant (p= <0.0001). Participants who had treatment initiated within one month of diagnosis had a higher survival rate (156; 59.6%) compared to those whose treatment was initiated after one month whereby all died. The observed difference was statistically significant (Log-rank p = 0.0019). Patients who abandoned treatment had 100% mortality, n=20. The difference in survival rate was statistically significant (Log rank p= <0.0001).

Table 3: Cox regression analysis for the factors associated with 3-year survival rate

Factor	Crude hazards ratio			Adjusted hazards ratio		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender						
Male	1	-	-		-	-
Female	0.9	0.56 -1.43	0.549			
Age groups (months)						
≤ 24	1	-	-	1	-	-
25 -48	1.85	1.1 - 3.1	0.019	1.8	0.9- 3.8	0.034
> 48	3.46	1.5 - 7.9	0.003	3.7	1.4 - 9.9	0.001
Laterality						
Unilateral	1	-	-	1	-	-
Bilateral	1.98	1.2 - 3.2	0.006	1.4	0.8 - 2.6	0.216

Eye protrusion						
Yes	5.44	3.1 - 9.5	<0.001	1.5	0.6 - 3.8	0.364
No	1	-		-	-	
Duration of symptoms (months)						
< 3	1	-	-	1	-	-
3-6	2.26	0.7- 6.7	0.144	2.0	0.8 - 5.0	0.136
>6	5.13	1.8 - 14.3	0.002	4.5	1.7 - 9.4	0.112
Total delay time (months)						
< 6	1	-	-	1	-	-
≥ 6	4.09	1.7 - 9.4	0.001	0.3	0.07- 1.5	0.157
Disease stage						
1	1	-	-	1	-	-
2	2.48	0.7- 8.2	0.136	2.9	0.8 - 10.1	0.083
3	6.40	2.1 - 18.8	0.001	4.4	1.4 - 13.3	0.008
4	25.59	8.9 - 73.4	<0.001	5.2	1.5- 17.7	0.008
Treatment completion						
Yes	1	-				
No	17.8	9.1 -34.8	<0.001	13.7	5.0 - 37.4	<0.001

On both univariate and multivariate cox regression analysis, participants aged more than 24 months at diagnosis, extraocular disease (stage 3 and 4) and failure to complete treatment were found to be associated with lower survival.

DISCUSSION

Survival rates for patients with retinoblastoma vary significantly worldwide. In high-income countries, recent reports indicate 3-year survival rates as high as 99.5%. However, in developing countries, the survival rate remains low, with recent reports indicating a 3-year survival rate of 57.3%[7]. This study found a 3-year survival rate of 52.3%, which is higher than the rates reported in Uganda by Kalinaki *et al*[12] and in Kenya by Gichigo *et al*[11] which showed 3-year survival rates of 41.1% and 26.6%, respectively. However; this survival rate is slightly lower compared to that reported by the global retinoblastoma group (2022), which showed a 3-year survival rate of 57.3% of children from lower-income countries[7].

The 3-year survival rate observed in this study is significantly lower compared to the 3-year survival rates of over 80% reported in high- and middle-income countries[10,13,14]. The lower survival rate in this study is attributed to late presentation, which is due to underdeveloped primary eye care in Tanzania. Patients with retinoblastoma are first seen at primary and secondary health facilities where most health workers may have inadequate knowledge and skill to identify and appropriately refer them for tertiary care as previously reported by Mafwiri *et al*[15]. This leads to delay in presentation and late initiation of treatment. It is also reported that children in low-income countries present with a more biologically aggressive form of disease, which could have attributed to lower survival rate seen in this study[10]. Nevertheless, the current 3-year survival rate of this study is higher compared to that previously reported in Tanzania in 2008 by Bowman *et al*[16], which showed 30-months disease free survival probability of 23%. This shows that more children with Rb are surviving more compared to how it was 14 years ago. The improvement in survival rates for these patients can be attributed with the availability of well-established paediatric oncology free services, and improved follow-up of these patients.

Age at diagnosis was identified as an independent predictor of the survival with, a dramatic decline in survival rates for participants diagnosed after the age of 24 months. This has been widely reported in previous studies[4, 17]. It was observed that, many children who were diagnosed after 24 months of life had extraocular disease compared to those diagnosed earlier, which may have contributed to lower survival rate, supporting that retinoblastoma typically starts early in life.

Participants with unilateral retinoblastoma in this study had higher survival rate compared to those with bilateral retinoblastoma. The 3-year survival rate for both unilateral and bilateral retinoblastoma in this study

is lower compared to that reported in Turkey by Özkan *et al*[14] and in Singapore by Saw *et al*[13]. However; the global retinoblastoma group study (2022)[10] showed no difference in 3-year survival with regard to disease laterality. The lower survival rate in patients with bilateral retinoblastoma in this study may be explained by a large proportion of participants (approximately two-third) with bilateral disease who had advanced disease (stage 3 or 4) at presentation compared to patients with unilateral retinoblastoma (46.1%).

Advanced disease at presentation and poor patient outcomes are related to increased lag time before initiation of Rb treatment. This study showed that patients who presented with duration of symptoms of more than 6 months from the time when the parents / caretaker noted the first symptom to the diagnosis of Rb had lower survival rate compared to those who presented with duration of symptoms of less than 6 months. This observation has been reported widely in different studies[1, 17-20]. The lower survival rate in participants with longer duration of symptoms greater than 6 months before diagnosis is related to the greater risk of extraocular extension and central nervous system metastasis leading to poor survival rate in these patients[1, 21]. This indicates that lowering the lag time can be the effective first step towards improving survival in Rb patients. This can be achieved via targeted awareness of Rb campaigns and education programs, strengthening of red reflex test practices at the primary eye care level and shortening of referrals chains to the Rb treatment centres.

The advanced and metastatic disease stage (i.e., stage 3 and 4) at the time of first presentation to the hospital was present in half of the patients. These participants demonstrated a lower 3-year survival rate and all patients with CNS metastasis died. Similar findings have been reported in various studies.[1, 4, 11, 18, 19, 21-23]. The poor survival rate in these patients is because the disease already had the extraocular extension and CNS metastasis where by the disease became untreatable.

Participants who abandon treatment showed the dismal outcome. The main reason for treatment abandonment in this study was the refusal of enucleation. Similar findings have been reported by other authors[22-25]. The lower survival rate in this study was due to extraocular diseases advancement and CNS metastasis. Adequate information about the natural history of the disease and the importance of timely treatment should be given to all parents / care givers and their families so they can accept treatment. In addition, strict follow-up is also important to ensure that patients complete the required treatment regime in a required time period. Adequate and continuous counselling of parents is also necessary to ensure that patients complete treatment.

Nearly a quarter of the participants received palliative treatment due to presence of distance metastasis at the time of presentation. Two thirds of patients underwent enucleation and among them more than half received neoadjuvant and adjuvant chemotherapy. The patients with stage two disease and above also received the adjuvant radiotherapy post enucleation. In patients with bilateral retinoblastoma majority underwent bilateral enucleation and in a few patients, the fellow eye was salvaged. In those cases, the additional local therapy treatment was done which included cryotherapy, thermotherapy, intravitreal mephalan injection and subtenon carboplatin injection. The treatment modalities used in this study indicate the delayed presentation in diagnosis of these patients.

The patients whose treatment was initiated more than one month of diagnosis had lower survival rate compared to those whose treatment was initiated within one month of diagnosis. For patients whose treatment was initiated after one month from the diagnosis, the main reason was the initial refusal of enucleation. The lower survival rate in this is due to late treatment initiation resulting into disease progression and metastasis. Continuous comprehensive counselling is necessary to help the parents and the society to make timely decision regarding treatment for their children.

STUDY LIMITATIONS

Like any other retrospective study, our study also faced the challenges of incomplete data, and we had to exclude all such patients from the analysis thereby reducing the sample size and power of the study. In addition, the study could have faced the problem of recall bias on parents and caregivers reporting the onset of symptoms.

CONCLUSION

The 3-year survival rate of patients with retinoblastoma in our setting was 52.3%. Age at diagnosis of >24 months, failure to complete treatment, and extraocular disease invasion were associated with a lower survival rate.

RECOMMENDATIONS

Efforts to improve survival rate by early diagnosis, timely referral and timely initiation of appropriate treatment are necessary. This can be achieved by raising awareness of the disease to the primary and secondary health care workers and the community at large. Additionally thorough counselling for parents and caregivers to ensure treatment acceptance is necessary.

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Availability of data and materials: The dataset generated during this study is available with the corresponding author and can be shared upon genuine request.

Competing interests: None to declare.

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