

Survival and Prognostic Factors of Kaposi's Sarcoma Patients Treated at a High Complexity Oncology Care Center

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Sobrevida e Fatores Prognósticos de Pacientes com Sarcoma de Kaposi Atendidos em um Centro de Assistência de Alta Complexidade em Oncologia

Supervivencia y Factores Pronósticos de Pacientes con Sarcoma de Kaposi Tratados en un Centro de Atención de Alta Complejidad en Oncología

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ABSTRACT

Introduction: The survival of Kaposi's sarcoma is still not well known because the few studies that evaluated it were mostly conducted with people living with human immunodeficiency virus (HIV). **Objective:** To assess survival and pre-treatment prognostic factors in patients with Kaposi's sarcoma associated or not with HIV. **Method:** Retrospective study conducted in a hospital cohort of 81 patients diagnosed with Kaposi's sarcoma between the years 2000 and 2014 treated at a high complexity care center in oncology in the city of Rio de Janeiro, Brazil. The probability of 5-year survival was estimated using the Kaplan-Meier method. Hazard ratios (HR) and respective 95% confidence intervals (95%CI) were estimated following Cox's semi-parametric model of proportional hazards. **Results:** The global 5-year survival was 50.9% (95%CI: 38.2-62.3). The factors associated with death were age ≥ 50 years (HR: 4.19; 95%CI: 1.5-11.29) and positive anti-HIV serology (HR: 5.82; 95%CI: 1.90-17.85). **Conclusion:** The cohort had low survival. The prognosis was influenced by age ≥ 50 years and positive anti-HIV serology, and these factors should be considered in the pre-treatment risk assessment.

Key words: Sarcoma, Kaposi; Survival Analysis; Prognosis; Cancer Care Facilities.

RESUMO

Introdução: A sobrevida do sarcoma de Kaposi ainda não é bem conhecida porque os poucos estudos que avaliaram-na foram, em maioria, conduzidos com pessoas vivendo com vírus da imunodeficiência humana (HIV). **Objetivo:** Avaliar a sobrevida e os fatores prognósticos pré-tratamento de pacientes com sarcoma de Kaposi associado ou não ao HIV. **Método:** Estudo retrospectivo realizado em uma coorte hospitalar de 81 pacientes diagnosticados com sarcoma de Kaposi entre 2000 e 2014, atendidos em um centro de assistência de alta complexidade em oncologia da cidade do Rio de Janeiro, Brasil. A probabilidade de sobrevida em cinco anos foi estimada por meio do método de Kaplan-Meier. O modelo semiparamétrico de riscos proporcionais de Cox estimou *hazard ratios* (HR) e respectivos intervalos de 95% de confiança (IC95%). **Resultados:** A sobrevida global em cinco anos foi de 50,9% (IC95%: 38,2-62,3). Os fatores associados ao óbito foram idade ≥ 50 anos (HR: 4,19; IC95%: 1,5-11,29) e sorologia anti-HIV positiva (HR: 5,82; IC95%: 1,90-17,85). **Conclusão:** A coorte apresentou sobrevida baixa. O prognóstico foi influenciado pela idade ≥ 50 anos e sorologia anti-HIV positiva, devendo esses fatores serem considerados na avaliação de risco pré-tratamento.

Palavras-chave: Sarcoma de Kaposi; Análise de Sobrevida; Prognóstico; Institutos de Câncer.

RESUMEN

Introducción: La supervivencia del sarcoma de Kaposi aún no se conoce bien porque los pocos estudios que lo evaluaron se realizaron, en su mayoría, con personas que viven con el virus de inmunodeficiencia humana (VIH). **Objetivo:** Evaluar la supervivencia y los factores pronósticos previos al tratamiento en pacientes con sarcoma de Kaposi asociado o no con VIH. **Método:** Estudio retrospectivo realizado en una cohorte hospitalaria de 81 pacientes diagnosticados con sarcoma de Kaposi entre 2000 y 2014 tratados en un centro de atención oncológica de alta complejidad en la ciudad de Río de Janeiro, Brasil. La probabilidad de supervivencia a cinco años se estimó utilizando el método de Kaplan-Meier. El modelo de riesgos proporcionales semiparamétricos de Cox estimó las razones de riesgo (HR) y los respectivos intervalos de confianza del 95% (IC95%). **Resultados:** La tasa de supervivencia general a cinco años fue del 50,9% (IC95%: 38,2-62,3). Los factores asociados con la muerte fueron edad ≥ 50 años (HR: 4,19; IC95%: 1,5-11,29) y serología positiva contra el VIH (HR: 5,82; IC95%: 1,90-17,85). **Conclusión:** La cohorte mostró baja supervivencia. El pronóstico estuvo influenciado por la edad ≥ 50 años y la serología positiva contra el VIH, y estos factores deben considerarse en la evaluación de riesgos previa al tratamiento.

Palabras clave: Sarcoma de Kaposi; Análisis de Supervivencia; Pronóstico; Instituciones Oncológicas.

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INTRODUCTION

Kaposi's sarcoma (KS) is a mesenchymal tumor caused by the human herpesvirus 8¹, that displays as a frequent multifocal vascular lesion in mucocutaneous sites but that can also affect lymph nodes and viscera². It was described for the first time in 1872, remaining as a rare tumor until the appearance of the human immunodeficiency virus – HIV in the beginning of the years 1980³. KS has four different forms: classic, endemic, iatrogenic and epidemic³. Considered the most aggressive form of the disease, the epidemic KS is associated to HIV and is more frequent among men that have sex with men¹.

Although highly active antiretroviral therapy has contributed to lower the incidence and mortality by KS¹, 41,799 new cases and 19,902 deaths were estimated for 2018 worldwide. For the same year in Africa, 32,446 new cases and 17,659 deaths by KS were anticipated, which corresponds to respectively 77.6% and 88.7% of the estimates of new cases and deaths for the entire world. KS is endemic in several countries of the South and East regions of the African continent, standing out Malawi, Mozambique, Uganda and Zambia which it is the main cause of death by cancer⁴.

In a study conducted in South Africa between 2000 and 2007 with 6,292 individuals living with HIV, 215 (3.4%) had KS: those who received highly active antiretroviral therapy presented rate of mortality of 25/100 persons-year and those who did not receive, 70/100 persons-year⁵. In Uganda, where KS is the second neoplasm most incident in the general population⁴, a study conducted with 404 individuals with HIV-associated KS showed likelihood of survival equal to 65.0% one year after the diagnosis and equal to 57.0% after two years⁶.

For 2018 in the USA 1,329 new cases of KS and 117 deaths have been estimated⁴. A study conducted in this country with 4,455 cases of KS in men with less than 55 years between 2000 and 2013⁷ showed tendency of drop of the incidence of the disease among Caucasians but not among Blacks, mainly for those in USA's Southern region for whom incidence growth occurred. In addition, in comparison with Caucasians, Blacks had more odds of dying by KS revealing the existence of geographic and racial disparities in the incidence and survival of KS in this country⁷.

In Brazil, between 1996 and 2010 the incidence of KS was 2.5 bigger than in the United States and even today, it is still the most frequent neoplasm in people living with HIV in the country⁸. For 2018, 778 new cases of KS were estimated and 137 deaths by this cause in Brazil⁴. A study conducted with 3,557 cases of the acquired immunodeficiency syndrome (aids) in a reference

center in the city of São Paulo estimated prevalence of KS equal to 60%¹.

The extensive literature review conducted by the authors revealed that the KS survival is not well known yet, since the few studies that evaluated it, mostly, were conducted with persons living with HIV. In order to collaborate to reduce this gap and contribute to the progress of the knowledge about the theme, the objective of this study was to evaluate the survival and pre-treatment prognostic factors of patients with KS consulted in a high complexity oncologic care center where patients with KS are treated, despite the HIV serological condition.

METHOD

Retrospective study developed in a hospital cohort consisting of patients diagnosed with KS between January 1 and June 30, 2014 and treated in a high complexity care oncology center, the National Cancer Institute José Alencar Gomes da Silva (INCA), located in the city of Rio de Janeiro, Brazil (N=81).

The source of information of the study was the database of the Cancer Hospital Registry. The patient chart was also reviewed to look for information not collected systematically in this Registry: anti-HIV serology, CD4 count, HIV viral load and highly active use of antiretroviral therapy that were registered in a single data collecting card and next, included in the database offered by the Cancer Hospital Registry.

The beginning of the follow up of each patient corresponded to the date of the KS histopathological diagnosis. For the five-year follow up, the following procedures were adopted in July 2019: survey of the database offered by the Cancer Hospital Registry, of the charts, of the Mortality Information System of the State of Rio de Janeiro and of the Extrajudicial Portal of Births and Deaths of the Judiciary Power of the State of Rio de Janeiro.

The variables investigated at the moment of diagnosis of KS were: gender (male or female), age (continuous and categorized per the median in <50 years and ≥50 years), race/skin color (categorized in Caucasian, and Black and/or Brown), education (categorized in none, incomplete elementary school and/or complete and high school and/or university), marital status (categorized in living with spouse and not living with spouse), anti-HIV serology (positive or negative), CD4 cells count (categorized in <200 cells/mm³ and ≥200 cells/mm³), undetectable HIV viral load (yes or no) and highly active antiretroviral therapy (yes or no).

Initially, an exploratory analysis of the data was conducted through the description of the variables in

the study population. For the continuous variable age, median, mean and respective standard deviation (SD) were calculated. For the other categorical variables, proportions were calculated, Fisher exact test or Pearson qui-square were used to compare the groups. For both tests, it was considered statistically significant $p < 0.05$.

To estimate the likelihood of five-year survival and its respective confidence interval of 95% (CI95%) it was applied the Kaplan-Meier method with the following criteria: i) initial event: histopathological diagnosis of KS; ii) final event: death, regardless of cause; iii) survival time: time between the initial and final events; and iv) censoring: missed cases during follow up and alive cases in the end of this period. Next, the functions of survival – global and according to the study variables – and their respective CI95% were estimated. To compare the survival curves, it was utilized the log-rank test, considering $p < 0.05$.

To evaluate the effects of the prognostic factors over survival time of the cohort, the hazard ratios (HR) were estimated and their respective CI95%, following the Cox semiparametric proportional hazards model. All the study variables were included together in the multi-variated analysis because they did not violate the presupposition of proportional hazards, evaluated through the test of supposition of proportional hazards, considering $p < 0.05$ in the software Stata version 15.0 where all the analyzes were performed.

The study complied fully with the norms included in the Resolutions of the National Health Council number 466 dated December 12, 2012 and number 510, dated April 7, 2016. It was approved by the Institutional Review Board of INCA on May 25, 2019, report number 3,347,762 and CAAE: 12620919,2,0000,5274.

RESULTS

Table 1 presents the sociodemographic and clinical characteristics of the study population. Males corresponded to 71.6% of the KS cases. Mean age at the diagnosis was 50 years and mean equal to 52.6% (SD = 18.7%). In addition, 62.2% of the cohort had positive anti-HIV serology.

When analyzing the distribution of the sociodemographic characteristics of the cohort according to the anti-HIV serology, the positives had the biggest proportion of male cases (82.6%) compared to negatives (54.1%). In relation to age-range, 73.9% of the positives had <50 years old compared to 7.1% of the negatives. Regarding education, 54.5% of the positives have completed high school and/or university compared to 28.6% of the negatives (Table 2).

Considering only those with positive anti-HIV serology at the diagnosis of KS, 15.4% presented

Table 1. Sociodemographic and clinical characteristics of the cases of Kaposi Sarcoma treated at a high complexity care reference center in oncology. Rio de Janeiro, 2000-2014 (N=81)

Variables	N	%
Gender		
Male	58	71.6
Female	23	28.4
Total	81	100
Age		
<50 years	37	45.7
≥50 years	44	54.3
Total	81	100
Race/skin color^a		
Caucasian	37	46.2
Black and/or brown	43	53.8
Total	80	100
Education^a		
None	05	6.3
Incomplete and/or complete elementary school	39	49.4
High school and/or university	35	43.3
Total	79	100
Marital Status^a		
Lives without spouse	47	59.5
Lives with spouse	32	40.5
Total	79	100
Anti-HIV serology^a		
Negative	28	37.8
Positive	46	62.2
Total	74	100

Captions: ^a Missing: race/skin color (N=1; 1.2%); education (N=2; 2.5%); marital status (N=2; 2.5%); anti-HIV serology (N=7; 8.6%).

undetectable HIV viral load, 60.0% had CD4 cells count <200 cells/mm³ and 10.5% were not in highly active anti-retroviral therapy (Table 2). However, the lack of information for these variables is of nearly 71.7%, 56.5% and 58.7%, respectively.

During five years of follow-up 49 (60.5%) censorships and 32 (39.5%) deaths were observed. The censored group consisted of 29 (59.2%) alive at the end of five years of follow up and 20 (40.8%) missed in the period. The missed cases had mean age at the diagnosis of 45.15 years (SD=18.55) and mean age of follow up of 22.7 months (SD=15.81). When compared to the other cases of the cohort, the group of patients missed to follow up had higher proportion of cases of men (90.0%; $p=0.04$) and age <50 years old (70.0%; $p=0.02$).

Table 2. Sociodemographic and clinical characteristics of the cases of Kaposi Sarcoma treated in a high complexity reference center in oncology according to the status of anti-HIV serology, Rio de Janeiro, 2000-2014 (N=81)

Variable	Anti-HIV Serology		p ^a
	Negative N (%)	Positive N (%)	
Gender			
Male	16 (57.1)	38 (82.6)	0.02
Female	12 (42.9)	08 (17.4)	
Total	28 (100)	46 (100)	
Age			
<50 years	02 (7.1)	34 (73.9)	<0.01
≥50 years	26 (92.9)	12 (26.1)	
Total	28 (100)	46 (100)	
Race/skin color^b			
Caucasian	15 (53.6)	16 (35.6)	0.15
Black and/or brown	13 (46.4)	29 (64.4)	
Total	28 (100)	45 (100)	
Education^b			
None	04 (14.3)	01 (2.3)	0.03
Incomplete and/or complete elementary school	16 (57.1)	19 (43.2)	
High school and/or university	08 (28.6)	24 (54.5)	
Total	28 (100)	44 (100)	
Marital Status^b			
Lives without spouse	13 (46.4)	31 (68.9)	0.08
Lives with spouse	15 (53.6)	14 (31.1)	
Total	28 (100)	45 (100)	
CD4 cells count^b			
<200 cells/mm ³	-	12 (60.0)	-
≥200 cells/mm ³	-	08 (40.0)	
Total	-	20 (100)	
Undetectable HIV Viral Load^b			
Yes	-	02 (15.4)	-
No	-	11 (84.6)	
Total	-	13 (100)	
Highly active antiretroviral therapy^b			
Yes	-	17 (89.5)	-
No	-	02 (10.5)	
Total	-	19 (100)	

Captions: ^ap-value corresponding to Fisher exact tests of Pearson chi-square; ^b Missings: race/skin color (N=1; 1.4%); education (N=2; 2.7%); marital status (N=1; 1.4%); CD4 cells count (N=26; 56.5%); undetectable HIV viral load (N=33; 71.7%); highly active antiretroviral therapy (N=27; 58.7%).

The mean time of follow up of the cohort was 33.5 (SD=23.1) months, being of 44.1 (SD=21.2) for the cases censored and of 18.9 (SD=17.1) for the cases of death.

Of the 32 deaths observed, 61.7% were males, 70.6% were ≥50 years old, 52.9% were Caucasian, 44.1% had completed high school and/or university, 54.5% lived

without spouse and 65.5% presented positive anti-HIV serology.

The probability of global survival of the cohort in five years was 50.9% (CI95%: 38.2-62.3) (Figure 1). Table 3 presents the conditional probability of five-years survival according to the clinical and sociodemographic variables

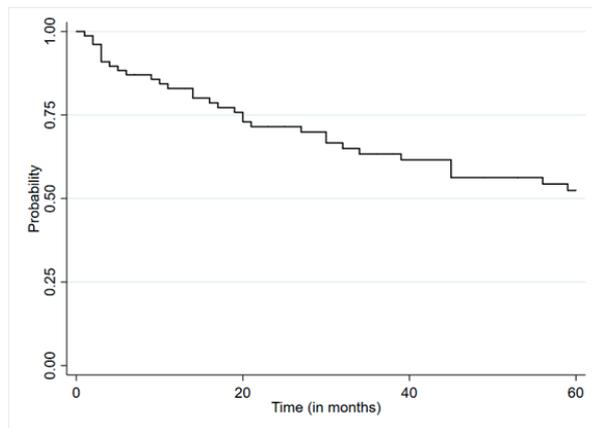


Figure 1. Kaplan-Meier curve showing five-years survival for the cohort of patients with Kaposi Sarcoma. Rio de Janeiro, 2000-2014

Table 3. Kaplan-Meier curve showing five-years survival for the cohort of patients with Kaposi Sarcoma. Rio de Janeiro, 2000-2014

Variables	Probability of survival (CI95%) ^a	p ^b
Gender		
Male	50.9 (38.2-62.3)	0.20
Female	40.8 (20.4-60.3)	
Age		
<50 years	66.6 (46.2-80.7)	0.06
≥50 years	39.8 (24.4-54.8)	
Race/skin color		
Caucasian	37.1 (18.7-55.6)	0.17
Black and/or brown	60.2 (43.2-73.5)	
Education		
None	20.0 (8.00-58.1)	0.40
Incomplete and/or complete elementary school	55.2 (36.3-70.5)	
High school and/or university	49.6 (29.9-66.6)	
Marital Status		
Lives without spouse	52.7 (35.2-67.6)	0.65
Lives with spouse	48.4 (29.1-65.3)	
Anti-HIV serology		
Negative	61.9 (40.5-77.5)	0.51
Positive	50.0 (32.7-65.0)	

Captions: ^aCI95%: confidence interval of 95% d; ^bp-value corresponding to the log-rank test.

of the study population. No significant differences among the groups were observed in any of the estimated survival curves.

Table 4 shows raw and adjusted HR estimated according to Cox proportional-hazards model. The multivariate model showed that, regardless of the other variables, age ≥50 years (HR=4.19; CI95%: 1.55-11.29)

and positive anti-HIV serology (HR=5.82; CI95%: 1.90-17.85) are prognostic factors for five-years death.

DISCUSSION

The objective of this study was to evaluate the survival and pre-treatment prognostic factors of KS patients treated in a Brazilian oncologic high complexity center. Its results show that in the end of five-years follow up the global survival was 50.9% and age ≥50 years and positive HIV-serology were independent factors of worse prognosis.

In the available literature, it is observed that most of the studies which evaluated the KS survival were of persons living with HIV treated in infectious diseases reference centers, which hampered the comparison of our results because 37.8% of the cohort patients had negative anti-HIV serology. However, it is worth mentioning that KS is an aids-defining neoplasm¹, recognized as the first HIV-associated opportunistic disease⁹ and the most prevalent tumor in this population¹⁰.

Based in this, the results of the present study regarding the limits of comparison show that KS five-years survival is lower than what was observed in studies conducted in Germany (96.8%)¹¹, UK (89.0%)¹² and Italy (79.1%)¹³ among persons living with HIV using highly active anti-retroviral therapy. It is believed that said difference is because the study was conducted in an oncology high complexity reference care center in Brazil where HIV-associated KS are usually referred to and the highly active anti-retroviral therapy was unsuccessful for the treatment of the neoplasm.

Based in the data of the Surveillance, Epidemiology, and End Results, official source of information for USA cancer surveillance, the five-years survival of individuals diagnosed with KS in 2011 was of 77.6%¹⁴ in the country. A Brazilian study conducted in a hospital cohort of 535 patients affected by several types of cancer between 2005 and 2012 reported KS five-years survival of approximately 65.0%¹⁵. All the patients with KS diagnosis of the referenced study had positive anti-HIV serology.

In comparison with the survival described by these studies, the survival of the present study is lower too. A reasonable explanation for this finding is that the great number of censorships for loss to follow up during the active follow up may have underestimated the survival, because it is likely that most of these censored cases is alive, otherwise, death would have been identified in the official information sources searched¹⁶.

Although the present study has not identified differences of the survival curves according to race/skin color, in the United States of America it was identified the existence of racial disparities for KS survival since

Table 4. Raw and adjusted Hazard Ratios for the cohort of patients with Kaposi Sarcoma. Rio de Janeiro, 2000-2014

Variables	Raw HR (CI95%) ^a	p ^b	Adjusted HR ^c (CI95%) ^a
Gender			
Male	1.00	0.83	1.00
Female	1.56 (0.77-3.17)		1.73 (0.56-5.30)
Age			
<50 years	1.00	0.58	1.00
≥50 years	1.99 (0.94-4.21)		4.19 (1.55-11.29)
Race/skin color			
Caucasians	1.00	0.34	1.00
Black and/or brown	0.61 (0.30-1.24)		0.55 (0.21-1.39)
Education			
None	1.00	0.53	1.00
Complete and/or incomplete elementary school	0.47 (0.15-1.44)		0.53 (0.12-2.22)
High school and/or university	0.55 (0.18-1.69)		0.58 (0.11-3.00)
Marital status			
Lives without spouse	0.85 (0.42-1.73)	0.68	0.66 (0.28-1.54)
Lives with spouse	1.00		1.00
Anti-HIV serology			
Negative	1.00	0.87	1.00
Positive	1.29 (0.59-2.82)		5.82 (1.90-17.85)

Captions: ^aCI95%: confidence interval of 95%; ^bp-value corresponding to the test of proportionality of risks; ^cHR: hazard ratio adjusted by all the variables.

among the 4,455 KS cases in males younger than 55 years diagnosed from 2000 to 2013, the five-years specific survival among Afro-Americans (63.3%) was significantly lower ($p < 0.01$) than among Caucasians (75.5%) and of the other races/ethnicities (74.0%)⁷.

However, it is worth mentioning that, in despite of statistical significance, the study shows that Blacks and/or Browns have high survival and lower risk of deaths in comparison with Caucasians. This result can be justified because of the categorization of the variable established due to the study small sample, since Black or Brown race/skin color were gathered in one category. Therefore, it is possible that Browns are masquerading the survival and risk of deaths of Blacks. For this reason, future studies and bigger samples than of the present study are necessary to investigate differences of survival in relation to race/skin color and possible causes.

In investigations conducted in infectious diseases reference centers with individuals living with HIV, some prognostic of worse survival were described: advanced staging of the tumor^{5,6,17,18}, concomitant systemic diseases^{5,6,17}, lung and liver compromise¹⁹, late diagnosis of HIV⁵, low CD4 count (< 200 cells/mm³)^{18,19} and serological detection of the human herpes virus type 8 at the diagnosis¹⁸. In this investigation, age ≥ 50 years and

positive anti-HIV serology were the only independent factors of worse prognosis identified.

Controversially, other studies did not identify age as a predictor of KS survival^{5,6,17-19}. The results of this study are different: because of control by several confounding variables, including anti-HIV serology, the effect of age ≥ 50 years over death was demonstrated. In addition, while comparing estimated survival curves according to age, the statistical significance was borderline – possibly because of the study small sample – which appears to corroborate the influence of this variable in the KS survival. It is believed, in the other hand, that the effect of advanced age over death is due also to the fact that this study was conducted not only with HIV-associated KS cases but also with other types of KS (unfortunately, unclassified in the chart), like the classic that affects individuals between 40 and 70 years preferentially²⁰.

Within the study limitations, the great number of censoring because of loss to active follow up stands out, which, further to the tendency of underestimating the likelihood of survival, it might have created a bias resulting from differential losses to follow up¹⁶. Furthermore, the survival evaluated was not disease specific as it was not possible to identify the cause of death of all the patients. The small cohort, although formed by all the patients

with KS treated according to the study scenario in the period investigated failed to grant accurate estimates of HR presenting wider CI95%. At last, the lack of registry of tumor staging in the chart and the scarce registries of CD4 cell count, HIV viral load and use of highly active antiretroviral therapy among those with positive anti-HIV serology made unfeasible the probable identification of these variables as prognostic factors.

Regardless of its limitations, the originality of the study is clear since KS survival was evaluated in a high complexity oncology care center where patients with KS are treated independently of the HIV serologic condition. It is believed that new studies are necessary, particularly multicentric because of the rarity of the neoplasm in order to have an overview of survival and prognostic factors of non-HIV associated patients with KS.

CONCLUSION

In the end of the five-years follow up, the global survival of the cohort was 50.9%. The age ≥ 50 years and the positive anti-HIV serology were independent prognostic factors for the death of the patients with KS consulted in a high complexity oncology care center. Therefore, because of its great predictive power, age and anti-HIV serology must be used to evaluate the pre-treatment risk of patients with KS.

CONTRIBUTIONS

Isabele da Rosa Noronha and Anne Karin da Mota Borges contributed for the analysis of the data, interpretation of the results and wording of the manuscript. Jeniffer Dantas Ferreira, Gelcio Luiz Quintella Mendes and Isabela da Rosa Noronha contributed for the critical review and wording. Rafael Tavares Jomar contributed for the conception and design of the study, analysis of the data, interpretation of the results and wording of the manuscript. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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