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ORIGINAL ARTICLE

Burkitt lymphoma in children and adolescents: a single-center analysis over a 30-year period

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Abstract

Introduction and Objectives: Burkitt lymphoma (BL) is a fast-growing and highly aggressive type of non-Hodgkin lymphoma. Nevertheless, 80-90% of patients on risk-adapted chemotherapy survive. The aim of this study was to characterize a pediatric population with BL in a center of reference, determine the 30-year incidence and calculate event-free and overall survival. **Methods:** We performed a retrospective and observational analysis of all patients diagnosed with BL between January 1993 and December 2022. Demographic and clinical data was collected. Patients were staged according to the St. Jude classification system and treated with different protocols according to risk stratification. A descriptive analysis, Portuguese central region incidence calculation and survival analysis were performed. **Results:** A total of 48 patients were included, 85% of which were male, with a mean age of 7.8 ± 3.7 years. Most cases (95.8%) were sporadic. The mean incidence rate was 0.34 cases per 100,000 person-years. Most (50%) patients were St. Jude stage III. A total of 41% were admitted to the pediatric intensive care unit (PICU), mostly due to tumor lysis syndrome (78.9%). The mortality rate was 6.3%. The mean follow-up was 87.8 ± 59.0 months with a 3-year event-free survival rate of 88.9% and overall survival rate of 93.2%. Subgroup analysis showed no differences between chemotherapy protocols. Higher uric acid was independently associated with PICU admission. **Discussion:** Our results regarding incidence and mortality are in line with previously-published literature. Notably, the last patient who died in our center was diagnosed 18 years ago. In conclusion, our results contribute to a better understanding of the epidemiology, clinical course and outcomes of BL in Portugal's pediatric population.

Keywords: Burkitt lymphoma. Survival. Pediatric oncology.

Linfoma de Burkitt em idade pediátrica: 30 anos de experiência de um centro terciário

Resumo

Introdução e Objetivos: O linfoma de Burkitt (LB) é um linfoma não-Hodgkin agressivo mas 80-90% das crianças submetidas a quimioterapia adaptada sobrevivem. Este estudo pretendeu caraterizar a população pediátrica com LB seguida num centro de referência, determinar a incidência em 30 anos e calcular a sobrevida global/sem eventos. **Métodos:** Análise retrospetiva de doentes com diagnóstico de LB no período de janeiro 1993 a dezembro 2022. Foram colhidos dados demográficos e clínicos. Os pacientes foram estadiados de acordo com a classificação de St Jude e tratados com diferentes protocolos de acordo com a estratificação de risco. Foi realizada análise descritiva, cálculo de incidência na região Centro de Portugal e análise de sobrevida.

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Resultados: Incluídos 48 doentes, 85% do sexo masculino, idade média de 7,8 ± 3,7 anos. A maioria (95,8%) foi do tipo esporádico. A taxa média de incidência foi de 0,34 casos/100.000 pessoas-ano. A maioria (50%) estava no estágio III de St. Jude. Um total de 41% foram internados na Unidade de Cuidados Intensivos Pediátricos (UCIP), sobretudo por síndrome de lise tumoral (78,9%). A taxa de mortalidade foi de 6,3%. A duração média do follow-up foi de 87,8 ± 59,0 meses, com uma taxa de sobrevida livre de eventos aos 3 anos de 88,9% e uma taxa de sobrevida global de 93,2%. A análise de subgrupos não identificou diferenças entre protocolos de quimioterapia. Nível de ácido úrico elevado é um preditor independente de admissão na UCIP.
Discussão: Em conclusão, os nossos resultados contribuem para uma melhor compreensão da epidemiologia, evolução clínica e *outcomes* do LB na população pediátrica em Portugal.

Palavras-chave: Linfoma de Burkitt. Sobrevida. Oncologia pediátrica.

Keypoints

What is known
– BL is an aggressive neoplasia with significant morbimortality.

What is added
– Incidence and survival in Portugal is further characterized.
– With new protocols, survival is the norm.

Introduction

Every year, around 400 children and adolescents are diagnosed with cancer in Portugal. Although it still is the leading cause of non-accidental death in this population, it is expected that more than 80% of these children and adolescents survive due to remarkable advancements in diagnosis and treatment. Leukemia, central nervous system malignancies and lymphoma are the most prevalent cancers[1,2].

Burkitt lymphoma (BL) is a rare, but highly aggressive, rapid-growing B-cell non-Hodgkin lymphoma. Three distinct subtypes of BL are recognized, with different epidemiology, risk factors and clinical presentations: endemic, sporadic and immunodeficiency-associated[3].

Sporadic BL occurs worldwide, with most cases in the United States and Western Europe. It is relatively more common in the pediatric population, accounting for 30% of pediatric lymphomas, with a peak incidence around the age of 10[4,5]. The most common site of involvement is intrabdominal, mainly the bowel[6]. The endemic subtype occurs in equatorial Africa and the most frequent presentation is a facial tumor that involves the mandible[6,7]. This subtype is closely associated with malaria and the Epstein-Barr virus. However, the underlying mechanisms and the relationship between the etiological factors and this subtype is still poorly understood[8]. Immunodeficiency-associated BL is most commonly seen in HIV-positive patients, but may also be seen in recipients of organ transplants and patients with congenital immunodeficiencies[4,6]. The most common sites of involvement include the lymph nodes, bone marrow and central nervous system[8].

Pathologically, BL is characterized by the translocation and deregulation of the MYC gene on chromosome 8, which encodes the c-myc protein transcription factor that regulates cell proliferation, differentiation and apoptosis, and therefore has the potential to involve multiple organ systems[4,9]. Overexpression of this c-myc protein leads to rapid B-cell proliferation, accounting for the rapid doubling time of BL tumor cells (between 24 and 48 hours)[10].

Histologically, BL has a “starry sky” appearance with benign histiocytes containing plentiful, clear cytoplasm dispersed among a background of basophilic tumor cells. High rates of proliferation and apoptotic cell death are generally observed (Ki-67+ fraction approaching 100 percent)[5,11].

Although a definitive diagnosis is confirmed through the histopathological evaluation of involved tissue (biological, immunophenotyping and genetic testing), imaging is essential throughout the entire clinical course of these patients: for diagnosis, staging and evaluating treatment response and potential therapy-related complications. The adoption of a multimodal approach is crucial in the management of BL with ultrasound, computed tomography, magnetic resonance imaging and positron emission tomography playing a role whenever necessary[12-15].

Chemotherapy is the mainstay of therapy in BL, with a similar approach regardless of the subtype. Given the effectiveness of chemotherapy regimens and often widespread disease at presentation, there is no role for radiation therapy. Current treatment options, with either a shorter or longer duration, employ intensive multiagent regimens[4,16].

Children and adolescents with BL require intensive treatments and prolonged hospitalization, which can have a negative impact on their quality of life[17]. Moreover, patients may experience several side effects from their treatments as well as the emotional distress associated with an oncological diagnosis[18].

Despite BL's aggressive behavior, 80 - 90% of patients on risk-adapted chemotherapy survive and reach adulthood in the developed world[19,20].

The primary aims of this study were to provide a demographic and clinical description of our population of BL patients and to calculate the overall, sex-specific and age-specific incidence rate of BL in the central region of Portugal. By way of secondary aims, we intended to evaluate prognostic factors and calculate overall survival and event-free survival.

Materials and methods

Study design and ethical approval

We performed a retrospective, observational and non-interventional study, based on the records of all children and adolescents with a diagnosis of BL, over a 30 year-period, at the Pediatric Oncology Department of the Centro Hospitalar e Universitário de Coimbra (CHUC). This unit provides care to all children and adolescents with cancer, diagnosed up to the age of 17 years old, in the central region of Portugal. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of CHUC.

Study population and instrument

The study sample included all children and adolescents with BL from the Pediatric Oncology Department – CHUC, during the period between January 1993 and December 2022 (30 years).

Data collection

All data was obtained from the patients' clinical and laboratory records. Analyzed variables included: age at diagnosis, sex, clinical presentation, St. Jude stage (stages I – IV), initial lactate dehydrogenase (LDH) and uric acid (UA), treatment protocol, therapeutic regimen and its duration, events (relapse/refractory disease, secondary cancer or death) and development. The resident population of the central region of Portugal by age and sex between 1993 and 2022 was provided by data collected from the Portuguese National Statistics Institute.

Therapy and evaluation

Patients were stratified by stage as defined by Murphy at the St. Jude Children's Research Hospital. This staging system is primarily based on the clinicopathological features of childhood BL: the number and anatomical pattern of disease sites, their resectability and the involvement of bone marrow (BM) and the central nervous system (CNS). Patients with resected stage I and resected abdominal-only stage II disease are treated with the group A regimen. Patients with unresected stage I/II, III or CNS-negative stage IV disease with fewer than 25% of blasts in BM are treated with the group B regimen. Patients with ≥ 25% blasts in BM or with CNS involvement are treated with the group C regimen.

At diagnosis, risk groups were stratified as A, B (I or II) or C (1 or 3) according to the tumor stage, resectability (complete/incomplete) and initial LDH level (</≥ two times the upper limit of normal) with treatment intensity adjusted according to the risk group.

Favorable-risk patients were defined as patients with stage I, stage II and low LDH stage III. High-risk patients were defined as patients with high LDH stage III and stage IV disease.

In our institution, over the last three decades, patients were treated using the LMB84 protocol from 1991 to 1995, the LMB89 protocol from 1996 to 2000 and the FAB/LMB96 protocol from 2001 to 2017.

More recently, rituximab has been added in children and adolescents with disseminated (high-risk) mature B-NHL in the Inter-B-NHL ritux 2010 protocol since 2018.

After treatment, patients were followed up at 30-day intervals during the first year, three-month intervals for one semester and six-month intervals until they had completed three years out of treatment. Thereafter they had yearly follow-up appointments.

Statistical analysis

Categorical variables were expressed as percentages and frequencies, while continuous variables were expressed as mean and standard deviation (SD).

We estimated incidence rates of BL (cases per 100,000 person-years) by sex (male and female), age group (0-4, 5-9, 10-14 and 15-19) and calendar-year (1993-2002, 2003-2012 and 2013-2022). We estimated the population at risk during the study period by extrapolating from the population of Portugal's central region, obtained in the national census. We calculated the incidence rates and their 95% confidence intervals.

Survival analysis was performed by plotting Kaplan-Meier survival curves. For the event-free survival

sub-analysis, the following factors were considered: relapse, progressive disease, secondary malignancy and death from any cause. Cox regression was used for subgroup survival analysis.

All potential risk factors for adverse events and death were investigated by univariate (chi square and Mann-Whitney, as appropriate) and multivariate analysis (logistic regression).

All p-values were two-tailed and considered significant if < 0.05. For statistical analysis, SPSS® Statistics version 29 was used.

Results

Demographic and clinical patients' characteristics

During the 30-year period, 48 children and adolescents were diagnosed with BL in our center. The distribution of new BL cases and the incidence rate (per 100,000) of BL in the central region of Portugal between 1993 and 2022 is shown in figure 1.

The new diagnosis mean was 1.6 cases per year and the mean age at diagnosis was 7.8 years (± 3.7). There was a predominance of the male sex (85%) and most cases were diagnosed in children aged five to nine (60%). All patients' demographic and clinical characteristics are summarized in table 1.

In terms of the clinical presentation of the disease, we registered two cases of immunodeficiency-associated BL (one case of AIDS and one of post-transplantation lymphoproliferative disease), while the rest were sporadic. There were no cases of endemic/African BL identified in our study.

The most common sites of involvement were the abdomen (54%) and jaw (25%). BL tumors arose on the nasopharynx and bone marrow (also called Burkitt cell leukemia) in 8.5% of cases and on the CNS in 4% of cases. During the initial investigation, infiltration of BM (39.6%), the kidney (39.6%) and the CNS (31.3%) was found.

Serum LDH levels at diagnosis were available for all patients with a mean serum LDH of 2321 IU/L (311-10730). Serum uric acid levels were available for 47 patients with a mean value of 455 μmol/L (71-1500).

Three patients (6%) received the LMB-84 protocol, 10 patients (21%) the LMB-89 protocol, 25 patients (52%) the FAB/LMB96 protocol and 10 (21%) the Inter-B-NHL ritux 2010 protocol. The mean treatment duration was 6.8 ± 2 months.

There were 19 (41%) admissions to the Pediatric Intensive Care Unit (PICU), most due to risk/tumor lysis syndrome (78.9%). There was no information regarding PICU admission for two patients diagnosed in 1993. All patients diagnosed with BL from 1993 to 2000 (n = 7) were admitted to the PICU. In contrast, since 2001 only 31% (n = 12) have undergone the same (p < 0.001).

The lethality rate was 6.3% (n = 3). The deaths were attributed to infection (n = 1, 1997), relapse (n = 1, 2005) and refractory disease (n = 1, 2005). In this 30-year period, two more events occurred, namely a relapse (1999) and secondary acute myeloblastic leukemia (2007). Both were subject to BM transplantation and are alive (out of treatment).

Table 1. Baseline demographic and clinical characteristics of children and adolescents with BL (n = 48)

	n	%
Types of BL		
Sporadic (non-African)	46	96
Immunodeficiency-associated	2	4
Sex		
Male	41	85
Female	7	15
Age group (years)		
(0-5)	10	21
(5-10)	24	50
(10-15)	13	27
(15-19)	1	2
Calendar year		
(1993-2002)	10	21
(2003-2012)	24	50
(2013-2022)	14	29
Clinical presentation (site)		
Abdomen	26	54
Jaw	12	25
Nasopharynx	4	8.5
Bone marrow	4	8.5
CNS	2	4
St. Jude staging		
II	1	2
III	24	50
IV	23	48
Therapeutic scheme		
B	25	52
C	23	48
Events		
Relapse/refractory disease	1	2
Secondary cancer	1	2
Death	3	6

Overall, age- and sex-specific BL incidence

Overall BL incidence rates in Portugal's central region did not vary significantly by year (Fig. 1). The incidence

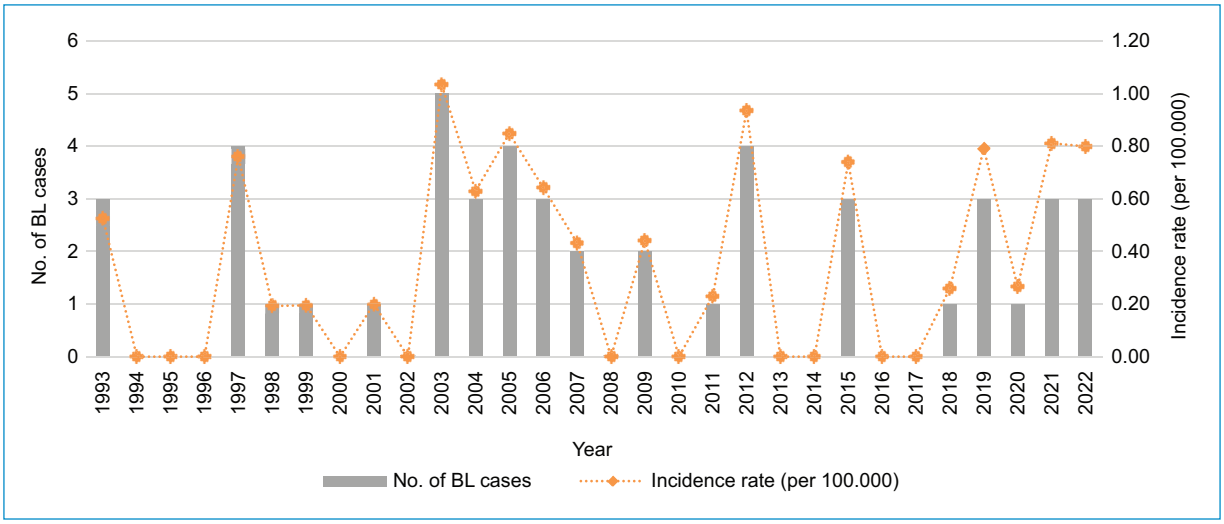

Figure 1. Distribution of BL cases per year in the central region of Portugal (n = 48).

rate was 0.34 cases per 100,000 person-years (95% CI 0.25-0.45) and was higher among boys than girls (0.55 vs. 0.11, respectively; p < 0.001), with this male predominance existing in all age groups (Fig. 2).

BL incidence rates increased rapidly with age from 0.34 cases per 100,000 person-years among children of age 0-4 years to 0.76 among those of age 5-9 years, then declined slightly among children aged 10-14 years before decreasing substantially at 15-19 years to the value of 0.03 cases per 100,000 person-years.

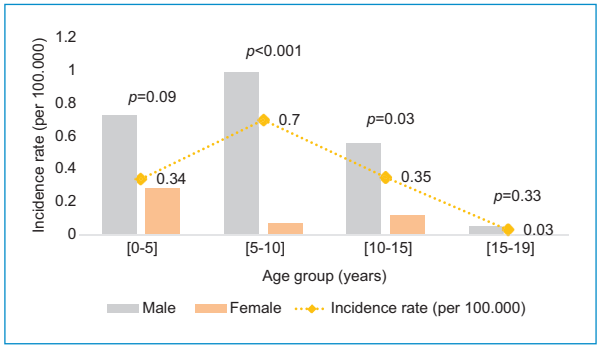

Figure 2. Age- and sex-specific incidence rates (per 100,000) of BL cases in the central region of Portugal (n = 45).

Survival analysis and prognostic factors

Average patient follow-up was 87.8 ± 59.0 months, with a 3-year event-free survival rate of 88.9% and a 3-year overall survival rate of 93.2% (Fig. 3). By analyzing patients based on regimens used (B or C), we observed a 3-year event-free survival rate of 91.8% vs. 85.2% (p = 0.543) and a 3-year overall survival rate of 95.8% vs 89.8% (p = 0.533), respectively.

We found that increased uric acid levels were independently associated with PICU admission (p = 0.006; OR 1.004, 95% CI 1.001-1.006). However, the risk of adverse events and death was not independently associated with PICU admission, LDH and/or uric acid level, age at diagnosis, sex, the protocol used or the length of treatment.

Discussion

Our results show an incidence rate of 0.34 BL cases per 100,000 person-years in the central region of Portugal, based on national data, which is in line with the published literature[21-23].

We also observed a slight increase in the incidence trend of BL in the last two decades compared to the first one, in keeping with previous reports[24]. The mechanisms underlying this trend are yet to be clarified.

The mean age at diagnosis and the mid-childhood peak incidence are in line with other studies conducted both in Portugal[25] and internationally[22,23,26-28].

A strong male predominance is a hallmark characteristic of this malignancy. These findings suggest that male sex itself may be an intrinsic risk factor for BL. This could be explained by the role of recessive genetic factors on sex chromosomes[29], such that a subset of X-chromosome genes can escape X-inactivation, protecting females from complete functional loss by a single mutation[30].

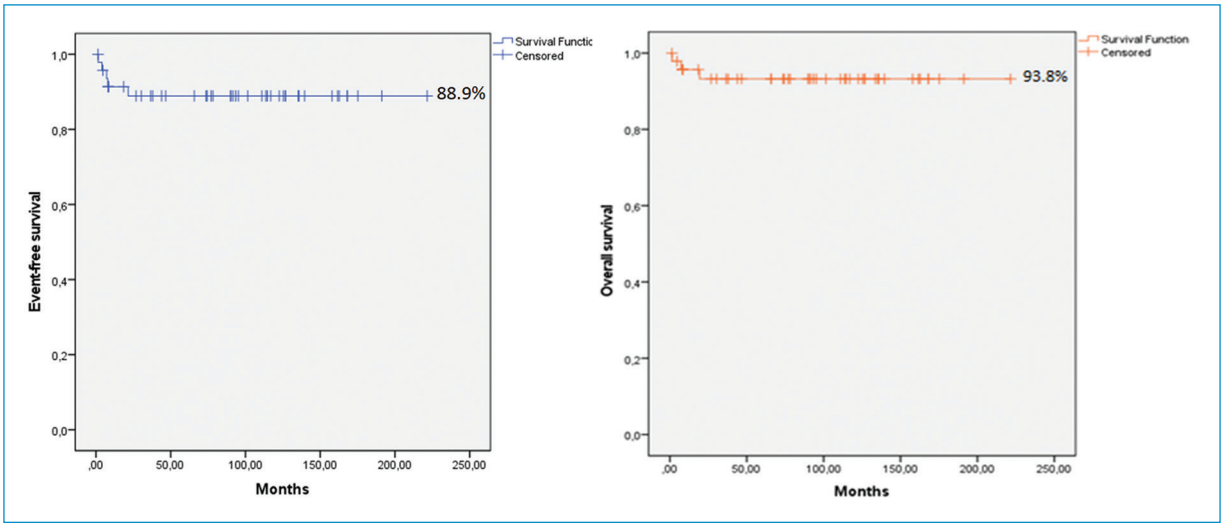

Figure 3. Kaplan-Meier event-free survival and overall survival curves of patients with BL (n = 48).

Most patients had a primary abdominal tumor. This is in line with it being the most frequent clinical presentation of the sporadic variant, which is the most prevalent type in Western Europe and the United States[5,6].

Serum LDH and UA levels seem to be important adverse prognostic factors. LDH levels in our study were higher when compared with previous studies from both European and non-European countries[26,31]. This could be explained by a larger tumor burden. However, there is insufficient available data to confirm this hypothesis. Our results support UA as a mark of poor prognosis, with higher levels being associated with a higher risk of admission to the PICU. However, we were not able to find a correlation between mortality and PICU admissions, LDH levels, UA levels, age at diagnosis, sex, the protocol used or the length of treatment. This may be justified by the low total number of adverse events and deaths in our population, limiting statistical inference.

Rasburicase, a recombinant urate oxidase, approved in February 2001, is recommended for the treatment and prophylaxis of acute hyperuricaemia[32]. In our study, tumor lysis syndrome or patients at a higher risk of tumor lysis syndrome were the most frequent cause of PICU admission. From 2001, admissions in this unit were significantly lower compared to the previous period. These findings suggest that rasburicase could be associated with a reduction in PICU admissions, since its use is now routine in BL treatment protocols in our center.

In the past few years, there has been substantial improvement in the prognosis of pediatric high-risk BL. Currently, the addition of dose-dense rituximab to FAB/LMB96 chemotherapy backbones is the main approach in children and adolescents with BL in Portugal, particularly in our center.

Overall and event-free survival were in line with the published literature, including two randomized trials for LMB96 and Inter-NHL ritux 2010 protocols[24,33,34]. Notably, the last patients who died were diagnosed with BL 18 years ago.

Chemotherapy-induced toxicity (mucositis, infection and myelosuppression) is a major endpoint but was not analyzed in our study, as this data was unavailable.

Our study is limited by the small sample, the fact that we only studied the population of a single center, the fact that it is retrospective and that cases are spread over a long period of time. Its strengths are that it was conducted in a center of reference, making the sample representative of the entire central region of Portugal.

Future studies relying on bigger samples and prospectively conducted, could result in a better evaluation and confirmation of our findings.

Conclusion

Our study shows that BL in the central region of Portugal has a male predominance and a peak incidence in mid-childhood. Due to our low mortality rate, we could not determine a correlation between the prognostic factors, admissions to the PICU, age or sex and death, but we managed to prove an independent association between increased UA levels and PICU admission.

In conclusion, our results contribute to the understanding of BL epidemiology, clinical course and outcomes in Portugal's pediatric population.

Authors' contribution

I. Pedrosa: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. A.M. Figueiredo: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. A.S. Simões: Conception and design of the study, report, review or other type of work or paper; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. I. Luz, M. Jerónimo, S. Silva, and A. Carvalho: Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. M. Brito: Conception and design of the study, report, review or other type of work or paper; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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