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Extranodal NK/T-Cell Lymphoma, Nasal Type of Head and Neck in a Pediatric Population: A Systematic Review

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ABSTRACT

Objective: This review aims to identify and evaluate the management options for the extranodal NK/T-cell lymphoma, nasal type of head and neck in the pediatric population.

Methods: The study was conducted based on a comprehensive literature review from 2009 to 2025. The following keywords were used: extranodal NK/T cell lymphoma and children and head and neck.

Results: The clinical data, including sex, age, symptoms, localization at presentation, correlation with EBV infection, treatment, and its outcome, were analyzed. A total of 64 patients were evaluated. Among these cases, the nasal site was the most involved region. Positive results for EBV infection were present in 100% of patients. The mortality rate in this study was 25%.

Conclusions: This systematic review highlights a clear male predominance, a pronounced geographic concentration of cases in East Asia, and underscores the diagnostic importance of EBV positivity in the diagnosis of ENKTL. In the case of the chronic course of destructive processes in aerodigestive organs with no improvement after standard treatment, NK-cell lymphomas should be considered in the differential diagnosis. Multimodal treatment strategies, particularly asparaginase-based chemotherapy with or without radiotherapy, are associated with improved outcomes, although disease-related mortality remains substantial. Given the limited number of pediatric cases and the heterogeneity of available data, further prospective, multicenter studies with standardized diagnostic and therapeutic approaches are essential to optimize management and improve long-term survival.

1 | Introduction

Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL) are the two primary categories of all lymphomas. NHLs are divided into B- and T-cell lymphomas and natural killer cell (NK) lymphomas. NKs are part of the innate immune system, acting as cytotoxic cells against damaged cells in the human body: cancer cells and cells infected with viruses. In terms of phenotypic characteristics, NK cells express the antigen CD56, and T cells express CD2 and CD3 [1]. Lymphoma is the third most frequent sinonasal malignancy, behind squamous cell carcinoma and adenocarcinoma. Hematolymphoid neoplasms account for 5%–15% of head and neck cancers. While the "nasal" and "nasal type" varieties of NK-cell lymphomas are very rare clinical entities in the United States and Europe, they are more common in East Asia and Latin America [2]. Extranodal NK/T-Cell lymphoma (ENKTL) is highly associated with the Epstein–Barr virus (EBV) infection. EBV appears to be an

Abbreviations: CAEBV, chronic active Epstein–Barr virus disease; EBV, Epstein–Barr virus; ENKTL, Extranodal NK/T cell lymphoma, nasal type; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NK, Natural killer cell

important factor to the pathophysiology of ENKTL, even though the exact mechanism is still unknown [3–6]. ENKTL is an aggressive malignancy that presents as a necrotic process. It primarily affects the nasal structures or the upper respiratory and upper digestive system organs. Infrequently, the other, extranasal sites of involvement are skin, soft tissues, testis, eyes, kidneys, or the gastrointestinal tract. Apart from the nasal cavity, the skin is the most commonly affected site by ENKTL [5]. The most common initial symptom is nasal obstruction, which may be accompanied by odorous discharge following ulcerative necrotic lesions or recurrent nose bleeding. Midface necrotic processes can affect the skin and mucosa of the nose, along with the nasal septum, turbinates, paranasal sinuses, and nasopharynx. Destructive lesions can extend to contiguous structures such as face skin, cheeks, orbits, the upper lip, palate and oropharynx. The disease often presents palatal ulcers, oromaxillar necrosis, and maxillary gingival ulcers that can transform into intraoral fistulas [6–8]. The diagnosis can be challenging since the clinical manifestation mimics chronic inflammation or reactive diseases. A biopsy is mandatory to confirm the diagnosis. The ENKTL is formed of atypical lymphoid proliferation with an angiocentric growth pattern, angiodestruction, and perivascular hyaline necrosis. There are numerous mitotic figures and areas of necrosis. The characteristic immunophenotype of nasal T/NK cell lymphoma is distinguished by a cytoplasmic CD3, CD2, and CD56 positivity along with the expression of cytotoxic molecules like granzyme B, perforin, and TIA-1 [2, 6]. The evidence of an EBV can be shown by in situ hybridization (ISH). A positive result for EBV is needed to confirm the diagnosis of ENKTL and helps to differentiate it from peripheral T-cell lymphoma [6]. Differential diagnosis of necrotic lesions of the midline of the face includes cocaine abuse, granulomatosis with polyangiitis, lymphomatoid granulomatosis, leishmaniasis, tertiary syphilis, or Langerhans cell histiocytosis. Metastases can develop during the disease course and spread to the skin, gastrointestinal tract, lymph nodes, or central nervous system. Bone marrow involvement is very rare and is diagnosed in 1.9%–16% of patients [8–10]. Bone marrow involvement indicates a high risk for hemophagocytic syndrome, which is a major complication that significantly reduces survival. This syndrome manifests as fever, pancytopenia with coagulopathy, splenomegaly and hemophagocytosis in bone marrow and liver [10].

The mean annual incidence rate of ENKTL in the adult population in the United States is 0.067 per 100,000, with higher rates observed in men compared to women, and an increase noted with age [11]. Most of the affected patients are adults, between the ages of 46–60 years, but it can also affect children and adolescents. Among children and adolescents, it is difficult to estimate a population-based incidence of NK/T-cell lymphomas owing to the lack of international registry data. Large-sample studies are not available due to the low incidence of ENKLT in this age group. According to a study by Termuhlen, NK/T-cell lymphomas constitute between 0.2% and 1.6% of newly diagnosed cases of NHL in the population 0–18 years old [12]. The youngest reported patient with ENKLT was 2 years old.

This review aims to identify and evaluate the management options for the ENKTL, nasal type of head and neck in the pediatric population.

2 | Methods

This study was elaborated in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The completed PRISMA 2020 checklist is provided in Supporting Table S1 [13]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251270794 [14].

2.1 | Search Strategy

A comprehensive literature search was conducted in MEDLINE (via PubMed) and Embase (via Ovid) using MeSH terms: extranodal NK/T-cell lymphoma, nasal-type OR ENKTL AND children OR pediatric OR adolescent AND head and neck. The time criterion of the reviewed papers was from 01.01.2009 to 30.11.2025. The authors used the 2009–2015 time frame because, before this period, the disease was defined according to earlier WHO classifications that used different diagnostic criteria. In addition, the availability of genetic testing for EBV was limited before this time in some countries, and immunohistochemical techniques were less advanced and less widely accessible. Consequently, studies published before 2009 are not fully comparable to those conducted under the updated diagnostic standards and laboratory capabilities.

2.2 | Selection Criteria

The study selection process was executed independently by three reviewers (A.G., I.B., and J.S.). All articles addressing the topic were screened through a full-text review. The studies were screened for inclusion using the following criteria: (1) cases diagnosed and pathology-confirmed as ENKTL, nasal type; (2) studies based on pediatric patients (patients aged 0–18 years); (3) head and neck involvement; (4) cases with CD3(+) and CD20(−); (5) cases with positive EBV testing. The criteria for exclusion included: (1) patients with ENKTL tumors located not in the head and neck region, (2) reviews based on the adult population (more than 18 years old), (3) cases without immunohistochemical phenotype information (CD3, CD20), and (4) patients with a negative EBV detection test. Disagreement was resolved in consensus with senior reviewers (I.B. and A.MM.).

2.3 | Data Extraction

The following data were extracted from the included studies: patient age, sex, clinical manifestations, immunohistochemical phenotype, genetic testing, radiological data, treatment, and long-term outcomes. The same two reviewers (A.G. and J.S.) independently performed the full-text screening, followed by data extraction, and any discrepancies were resolved in consensus with the senior reviewers (I.B. and A.MM.).

2.4 | Study Quality Assessment

The risk of bias within the included studies was evaluated by two authors (A.G. and J.S.) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, assessing possible bias in four different categories: patient selection, index test, reference standard, and flow and timing [15]. Methodological quality of the included studies was assessed independently by two reviewers using the Joanna Briggs Institute (JBI) critical

appraisal tools [16]. The JBI checklist for case reports was applied to single-patient publications, while the checklist for case series was used for retrospective case series, observational cohort studies, and single-arm clinical studies. Discrepancies were resolved by consensus. The results of the quality assessment are presented in Supporting Table S2.

3 | Results

A total of 67 studies were identified through the literature search. After removal of duplicates and irrelevant papers, 49 studies underwent full-text screening. Four articles were excluded due to nonlaryngological localization of disease, 23 studies were rejected because they involved both children and adults, 7 articles addressed other ENKTL tumors, 3 papers were excluded due to negative EBV testing, and 2 papers lack immunonophenotyping. The selection process is illustrated in Figure 1. Ultimately, 10 articles were included. Results from this retrospective review are presented in Table 1. The analyzed clinical data include sex, age at diagnosis, symptoms, localization at presentation, immunohistochemical phenotype, correlation with EBV infection treatment, and survival.

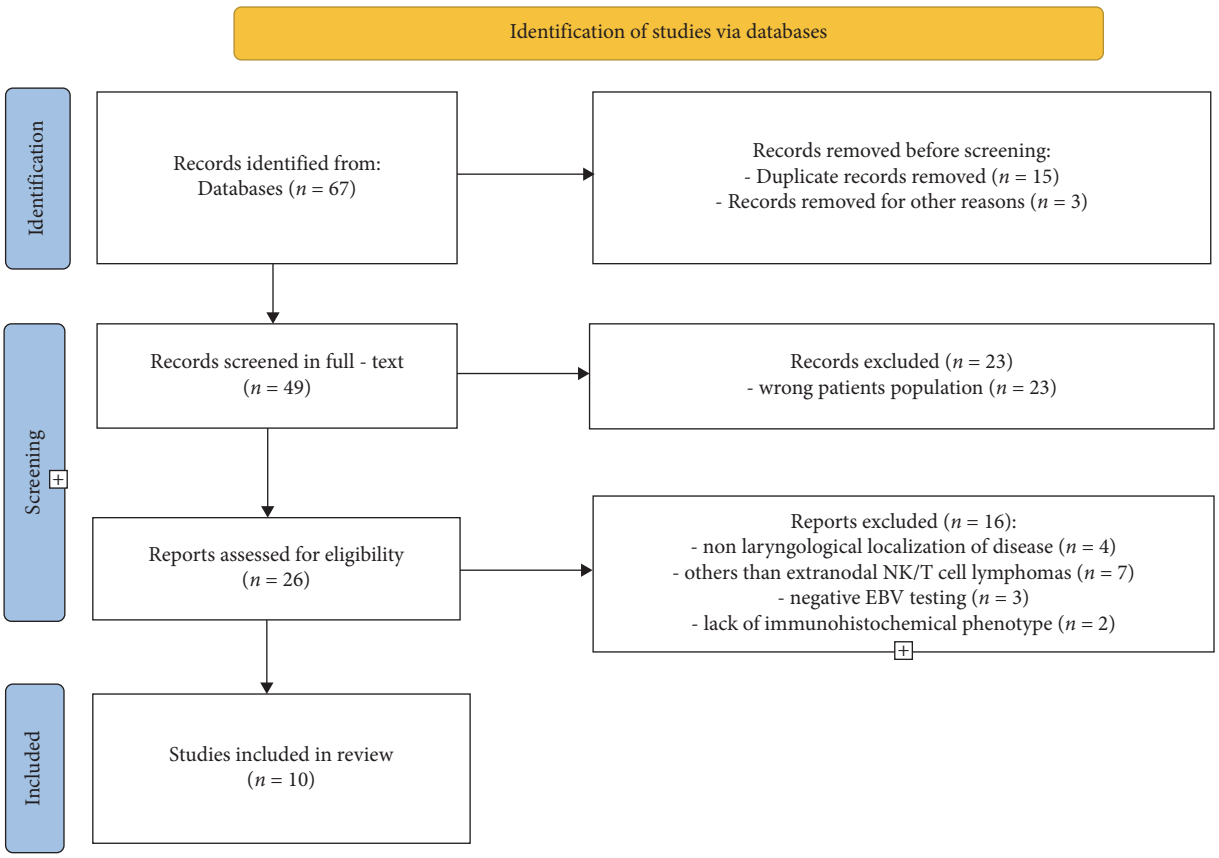
3.1 | Demographic Characteristics

In 10 articles [17–26], 64 patients were evaluated. The male group consisted of 42 boys, and the female group comprised 22 girls. Male-to-female ratio was 1.9:1. Mean age was 10.6 years with an age range of 2–17 years. The group of evaluated patients consisted of 89% children from China (57/64), and the rest of the group from the United States (2/64), Europe (2/64), Tunisia (2/64), and one patient from India. In the USA group, one child was African-American, one was Spanish, and one was Latin. Among these cases, the nasal site was the most involved region. The most frequently involved organs are presented in Table 2.

All 64 patients were tested for EBV infection, and all tested positive. EBV viral load determination by polymerase chain reaction (PCR) was the preferred diagnostic method for ENKTL. All evaluated patients demonstrated CD3 positivity and CD20 negativity. In most cases, cytotoxic markers, including granzyme B and TIA-1, were positive. Chemotherapy constituted the primary treatment modality for ENKTL. Chemotherapy was administered to 84% (54/64) of patients; 54% (35/64) received chemotherapy alone, while 28% (18/64) received chemotherapy combined with radiotherapy. One patient underwent chemotherapy and hematopoietic stem cell transplantation (HSCT). Radiotherapy as a sole treatment was implemented in 4% (2/64) of cases. Five children did not receive any treatment, and the treatment status of three patients remains unknown. Survivability was also assessed: 70.5% of patients (36/51) are disease-free, while 25.5% (13/51) died.

4 | Discussion

With advances in immunohistochemical techniques and the recognition of EBV as a key etiologic factor in the pathophysiology of ENKTL, the diagnostic terminology has also been



PRISMA flow diagram of the literature search strategy.

FIGURE 1 | Literature search strategy.

TABLE 1 | Clinical features of ENKTL in children and adolescents.

Study	No of patients	Sex	Country	Organ involvement	EBV testing	CD3	CD20	Granzyme	Tia	Treatment	Survival	QUADAS-2
McEachron et al. [17]	1	F	USA	orbital mass with intracranial extension	+	+	−	+	NA	C + R	disease-free	3
Gungor et al. [18]	1	M	African American in USA	nasal cavity, nasopharynx, larynx, and trachea	+	+	−	+	+	C + R	disease-free	3
Huang et al. [19]	17	13M 4F	China	nasal cavity (11/17), Pharynx (3/17). orbit mass (2/17) skin lesions (1/17) multiple organs involvement (1/17) Palate (3/17)	17x (+)	17x (+)	17x (−)	+	+	C 8/17 C + R 5/17 R 1/17 Untreated 1/17 NA 2/17	4—died, 13—disease-free	3
Maciejka-Kemblowska et al. [20]	2	2 F	Poland	Skin lesions (2/2) palate 1/2 Tonsils 1/2 nasopharynx 1/2 Bone marrow (1/2)	2x (+)	+ +	− −	+ +	NA	C 2/2	1—died 1—disease-free	3
Geetha et al. [21]	1	M	India	palate nasal cavity nasopharynx maxillary sinus ethmoid sinus frontal sinus lymphadenopathy	+	+	−	+	NA	C	disease-free	3
Wang et al. [22]	22	15 M 7 F	China	nasal cavity (12/22) nasopharynx (3/22) maxillary sinus (1/22) skin lesions 2/22 lymphadenopathy (4/22)	22x (+)	22x (+)	22x (−)	+	22x (+)	C 13/22 C + R 5/22 R 1/22 Untreated 3/22	7—died 15—disease-free	3
Shen et al. [23]	4	3M 1F	China	4x nasal cavity	4x (+)	4x (+)	4x (−)	4x (+)	4x (+)	C + R 4/4	4—disease-free	3
Oh et al. [24]	1	M	China	nasopharynx	+	+	−	+	+	C + R	disease-free	3
Zeglaoui and Sriha [25]	2	M F	Tunisia	nasal cavity (1/2) maxillary sinus(1/2) ethmoid sinus (1/2) orbit (1/2) tonsil (1/2) palate (1/2)	2x (+)	+	− −	NA	NA	C 2/2	1—died 1—disease-free	3
Guan et al. [26]	13	7M 6F	China	nasal cavity (8/13) orbit(3/13) skin lesions 3/13 Fever 5/13	13x (+)	13x (+)	13x (−)	13x (+)	13x (+)	C 9/13 C + HSCT 1/13 C + R 1/13 Untreated 1/13	NA	3

Note: C, chemotherapy; C + R, chemotherapy combined with radiotherapy; R, radiotherapy.
Abbreviations: HSCT, hematopoietic stem cell transplantation; NA, not available.

TABLE 2 | The most frequently involved organs.

Organs involvement	$n = 64$	Percentage
Nasal cavity	38/64	59%
Skin of face	8/64	12.5%
Orbit	7/64	10.9%
Nasopharynx	7/64	10.9%
Oral cavity	6/64	9%
Lymph nodes	4/64	6.25%
Sinuses	3/64	4.6%
Larynx and trachea	1/64	1.5%
Intracranial progression	1/64	1.5%

revised. According to the WHO 2022 classification, EBV detection is now an essential diagnostic criterion, and pediatric cases are designated as EBV-positive NK/T-cell lymphomas of childhood [27]. This evolution justifies the strict inclusion criteria applied in the present systematic review, in which EBV positivity was mandatory, ensuring diagnostic homogeneity and comparability across studies. EBV-related neoplasia is accurately diagnosed by the ISH of EBV-encoded RNA (EBER) using biopsy samples and EBV viral load tests using blood samples. Apoptosis of EBV-related lymphomatoid cells releases EBV DNA into the peripheral blood. Measuring the copy number of the EBV genome in whole blood is important for predicting the prognosis before the treatment, monitoring of the response to treatment, and follow-up after treatment [22]. In primary infection, EBV in saliva infects B cells, epithelial cells of Waldeyer's ring, and T/NK-cells [5]. In some cases, it can take the clinical course as an extended process called systemic active chronic EBV disease (CAEBV) [6]. It mainly affects the pediatric population, increasing the risk of ENKTL and systemic EBV-positive T-cell lymphoma during childhood [5, 6, 8]. Several potential mechanisms of oncogenesis caused by EBV have been described in the literature. EBV-infected NK cells produce IL-2, IL-9, IL-10, and cytokines that promote proliferation and the overexpression of the oncogenic latent membrane protein 1 (LMP1) [5, 6]. Activation of the NF-κB signaling pathway is another potential oncogenic EBV-mediated mechanism that promotes survival of pathologic cells and inhibition of apoptosis [28]. The mechanistic studies have also demonstrated that the EBV-encoded microRNAs (EBV-miRNAs) are associated with the development and prognosis of lymphoma. GO and KEGG pathway analysis indicate that genes targeted by the upregulated miRNAs are significantly enriched in multiple tumor-related pathways including MAPK signaling pathway, Wnt signaling pathway, the Focal adhesion, and ErbB signaling pathway, while genes targeted by the downregulated miRNAs are significantly enriched in Axon guidance and VEGF signaling pathway. In addition, the higher expression of EBV-miRNA is related to shorter overall survival [29]. The genetic analyses by Kimura indicate that DDX3X, TP53, STAT3, and BCOR1 are driver genes that are frequently mutated in patients with ENKTL and CAEBV. This suggests that EBV-infected T/NK cells evolutionally expand with driver gene mutations and that mutations in DDX3X are important for the development of lymphoma in patients with CAEBV. Activation-induced cytidine deaminase (AID), which belongs to the APOBEC3 protein family and induces somatic hypermutations and class switch recombination, is a candidate cause of such host gene mutations [30]. Patients with CAEBV usually develop fever, lymphadenopathy, and hepatosplenomegaly. Some children with CAEBV present cutaneous symptoms of hydroa vacciniforme lymphoproliferative disorder or severe mosquito bite allergy [6, 26]. A positive correlation between the incidence of cancer and CAEBV has also been proven in many other malignancies, such as Burkitt lymphoma, nasopharyngeal cancer, other aerodigestive cancers, and even gastric cancer [31]. Apart from molecular testing, the diagnosis is also based on a biopsy with immunohistochemistry examination and on imaging studies (computer tomography, magnetic resonance imaging, positron emission tomography). The radiological features of ENKTL in adolescents are not specific but give information on the extent of its destructive process [23, 32]. The diagnosis process of ENKTL is often prolonged due to the similarity of this pathology to chronic inflammation or reactive diseases. The disease is very rarely diagnosed among Caucasian patients. A striking geographic imbalance was identified, with 89% of cases originating from China, reflecting the known epidemiology of ENKTL, which shows a markedly higher incidence in East Asia and parts of Latin America. In contrast, only isolated pediatric cases have been reported in Europe and the United States. This systematic review analyzed 64 pediatric patients with ENKTL involving the head and neck region. A clear male predominance (male-to-female ratio, 1.9:1) was observed, consistent with both pediatric and adult ENKTL cohorts [11, 19, 22]. The mean age at diagnosis was 10.6 years, confirming that this aggressive lymphoma can affect children across the entire pediatric age spectrum. The most common sites of ENKTL in children and adolescents are the nasal and paranasal areas [11, 19, 22]. In this study, the nasal cavity was affected in most of the cases (59%), followed by the skin of the face, orbit, nasopharynx, oral cavity, lymph nodes, sinuses, and larynx. ENKTL is characterized by vascular damage, necrosis, and progression of the extensive midfacial destructive process. The treatment is based on the location of the primary focus, progression of the disease, and on the Ann Arbor staging system [33]. Chemotherapy constituted the main treatment modality in the analyzed cohort, administered to 84% of patients. Combined chemotherapy and radiotherapy were frequently used, particularly in survivors, reflecting current treatment paradigms. Modern ENKTL regimens are based on asparaginase-containing chemotherapy, including DDGP (dexamethasone, cisplatin, gemcitabine, and pegaspargase), SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), and GELOX (gemcitabine, L-asparaginase, and oxaliplatin) protocols [34–41]. The main component of these regimens is asparaginase or its pegylated form. It is considered to be the most important drug for the treatment of ENKTL as it induces apoptosis of NK-cells in vitro [42, 43]. The outcomes of this treatment have significantly improved with the addition of modern radiotherapy techniques and the addition of L-asparaginase into chemotherapy regimens [39]. NK/T-cell lymphomas are radiosensitive. Radiotherapy is proven to be an efficient treatment for localized, early-stage (I/II) ENKTL [44, 45]. Various combined chemoradiotherapy strategies (sequential, sandwich, and concurrent) have been described, although no consensus exists regarding the optimal approach. In this review, among surviving patients, combined chemoradiotherapy and chemotherapy alone were both commonly employed, whereas radiotherapy alone was

rarely used [38, 46]. In the study, among those children who survived, 13 were treated with chemotherapy combined with radiotherapy, 15 with sole chemotherapy, and 2 with sole radiotherapy. Four children did not receive the treatment and died. HSCT (auto or allo) offers a potentially good outcome, but the treatment is associated with a high rate of complications and the side effects of transplantation dominate over the benefits of the treatment [6, 47–49]. Antiviral drugs are not efficient in CAEBV. The future treatment depends on the outcomes of studies and trials based on monoclonal antibodies (PD1 Inhibitors, Daratumumab, Brentuximab) and signaling pathway inhibitors (PI3K Pathway Inhibitors, Jak/Stat Pathway Inhibitors) [50–52]. The Ann Arbor staging system is useful not only for management but also for prognosis [33]. Depending on the therapy implemented and stage by Ann Arbor, 5-year survival rates range between 40% and 65% in adults and chemoradiotherapy shows the most satisfactory treatment outcomes [29]. The prognosis is poor, especially if the unfavorable prognostic factors are met such as age > 60 years, stage III/IV disease, distant lymph node involvement, and non-nasal-type disease [8]. The invasion to adjacent tissues and metastasis to distant organs are also described in the literature [19]. Ethnicity had no prognostic correlation with survival [53]. The overall survival of pediatric patients is 77% for those with stage I/II disease and 36%–59% for those with advanced disease [11, 12]. In our study, survival rate was 75%. Survival data were available for 51 patients, with an overall survival rate of approximately 75%, consistent with published pediatric series. Thirteen children died, four of whom did not receive any treatment, underscoring the aggressive nature of the disease and the importance of early diagnosis and therapy. There are several limitations of this study. As the ENKTL is a very rare disease, the number of included study participants is relatively low. Due to the retrospective nature of this study, some data are missing, like long-term follow-up. Additionally, the geographic concentration of cases restricts the generalizability of findings.

5 | Conclusions

This systematic review highlights a clear male predominance, a pronounced geographic concentration of cases in East Asia, and underscores the diagnostic importance of EBV positivity in the diagnosis of ENKTL. In the case of the chronic course of destructive processes in aerodigestive organs with no improvement after standard treatment, NK-cell lymphomas should be considered in the differential diagnosis. Multimodal treatment strategies, particularly asparaginase-based chemotherapy with or without radiotherapy, are associated with improved outcomes, although disease-related mortality remains substantial. Given the limited number of pediatric cases and the heterogeneity of available data, further prospective, multicenter studies with standardized diagnostic and therapeutic approaches are essential to optimize management and improve long-term survival.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information 1. Supporting Table S1 contains the PRISMA 2020 checklist, detailing compliance of the present manuscript with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The checklist specifies where each reporting item is addressed within the manuscript, ensuring transparency and methodological rigor.

Supporting Information 2. Supporting Table S2 presents the methodological quality assessment of the studies included in this systematic review, evaluated using the Joanna Briggs Institute (JBI) critical appraisal tools for case reports and case series. This table summarizes the risk of bias across predefined domains and supports the overall reliability of the included evidence.