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Review Article

Cardiovascular Complications Due to Treatment Regimens in Pediatric Lymphoma Patients: A Systematic Review

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Abstract

Background: Lymphoma is among the most common malignancies in children, and improved survival has increased the importance of treatment-related late effects. Cardiovascular complications may result from the lymphoma itself or from chemotherapy and radiotherapy and can occur during treatment or years after exposure. This systematic review summarizes cardiovascular complications associated with pediatric lymphoma and its treatment.

Materials and Methods: The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. PubMed, EMBASE, and the Cochrane Library were searched from January 1, 1990, through July 20, 2024. Eligible studies included patients younger than 18 years with Hodgkin lymphoma or non-Hodgkin lymphoma and evaluated cardiovascular complications associated with chemotherapy and/or radiotherapy. Two reviewers independently screened studies, extracted data, and assessed methodological quality. Because of substantial clinical and methodological heterogeneity, findings were synthesized qualitatively.

Results: The search identified 930 records, of which 67 were considered potentially eligible after title and abstract screening. Following full-text assessment, 11 studies met the inclusion criteria. Reported cardiovascular outcomes included cardiomyopathy, ventricular dysfunction, arrhythmias, coronary artery disease, valvular abnormalities, pericardial disease, and other vascular complications. Anthracycline exposure was consistently associated with cardiotoxicity, while mediastinal radiotherapy was associated with important long-term coronary, valvular, and conduction abnormalities. Studies evaluating dexrazoxane suggested a cardioprotective effect without compromising antitumor efficacy.

Conclusion: Cardiovascular complications are an important long-term concern in children and adolescents treated for lymphoma. The available evidence supports risk-adapted cardiovascular surveillance during treatment and long-term survivorship, with particular attention to cumulative anthracycline exposure and mediastinal radiotherapy. Larger prospective studies are needed to define standardized surveillance strategies and clarify the long-term cardiovascular effects of contemporary treatment regimens.

Keywords: Antineoplastic Agents, Cardiovascular Diseases, Drug-Related Side Effects and Adverse Reactions, Lymphoma, Radiotherapy

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Introduction

Lymphoma is among the most common pediatric malignancies and accounts for approximately 10–15% of childhood cancers. In the United States, the incidence of lymphoma among children is approximately 25 cases per million, with nearly 2,000 new diagnoses reported annually (1, 2). Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are hematologic malignancies arising from lymphoid tissue (3). Pediatric lymphoma presents distinctive diagnostic and therapeutic challenges because of its heterogeneous clinical manifestations, variable treatment responses, and potential for long-term treatment-related complications. Lymphoma can involve lymph nodes, spleen, bone marrow, and extranodal sites and may also affect the cardiovascular system (4). Nonspecific symptoms can delay diagnosis and may overlap with manifestations of cardiovascular disease (5, 6).

Cardiovascular complications are clinically important in pediatric lymphoma because they may influence diagnosis, treatment selection, acute management, and long-term survivorship. Symptoms such as chest pain, dyspnea, fatigue, and palpitations may be nonspecific and can be attributed to the underlying malignancy or its treatment. Consequently, cardiovascular complications may be underrecognized without systematic assessment and appropriate follow-up (7).

The cardiovascular system may be affected by chemotherapy and radiotherapy used to treat pediatric lymphoma. Recognition of treatment-related cardiovascular toxicity is therefore important for risk stratification, surveillance, prevention, and early intervention. Anthracyclines are central components of many lymphoma treatment regimens but are associated with dose-dependent cardiotoxicity, including myocardial dysfunction and heart failure (8, 9). The purpose of this systematic review was to summarize the available evidence on cardiovascular complications in pediatric lymphoma, with particular emphasis on complications associated with chemotherapy and radiotherapy.

Material and Methods

Literature Search

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. Two reviewers (ME and GM) independently searched PubMed, EMBASE, and the Cochrane Library from January 1, 1990, through July 20, 2024. The search covered studies published within this period and focused on pediatric lymphoma, cardiovascular complications, chemotherapy, cardiotoxicity, and radiotherapy. The database-specific strategies were based on combinations of controlled vocabulary and free-text terms. For PubMed, the core strategy was: (Lymphoma OR Hodgkin Disease OR Non-Hodgkin Lymphoma) AND (Child OR Adolescent OR pediatric OR paediatric) AND (Cardiovascular Diseases OR cardiotoxicity OR cardiac OR cardiovascular) AND (Antineoplastic Agents OR chemotherapy OR anthracycline OR doxorubicin OR Radiotherapy OR radiation). For EMBASE, equivalent Emtree terms and free-text terms were combined using: (lymphoma OR Hodgkin lymphoma OR non-Hodgkin lymphoma) AND (child* OR adolescent* OR pediatric* OR paediatric*) AND (cardiovascular OR cardiac OR cardiotoxicity OR cardiomyopathy) AND (chemotherapy OR anthracycline* OR doxorubicin OR radiotherapy OR radiation). For the Cochrane Library, the corresponding terms were: lymphoma AND (child* OR pediatric* OR adolescent*) AND (cardiac OR cardiovascular OR cardiotoxicity) AND (chemotherapy OR anthracycline* OR radiotherapy). The search date was July 20, 2024.

Eligibility Criteria

Randomized controlled trials and cohort studies were eligible. Studies had to include patients younger than 18 years with confirmed HL or NHL, irrespective of disease stage or previous therapy, and evaluate cardiovascular complications associated with chemotherapy and/or radiotherapy. Ongoing studies, interim analyses, studies with fewer than 10 participants per study arm, reviews, letters, commentaries, case reports, conference abstracts, preclinical studies, and articles not published in English were excluded.

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Study Selection, Quality Assessment, and Data Extraction

Two reviewers (ME and GM) independently screened titles and abstracts against the predefined eligibility criteria. Potentially relevant articles underwent full-text assessment. Disagreements were resolved by consensus, with involvement of a third reviewer when necessary. The same reviewers independently extracted study characteristics and cardiovascular outcomes and assessed methodological quality. The methodological quality of cohort studies was evaluated using the Newcastle–Ottawa Scale. Because of substantial heterogeneity in study designs, treatment exposures, follow-up durations, and outcome definitions, a meta-analysis was not performed and a qualitative synthesis was undertaken.

Results

The study-selection process is summarized in Figure 1. The literature search identified 930 records. After title and abstract screening, 67 records were considered potentially relevant and underwent full-text assessment. Eleven studies met the inclusion criteria and were included in the qualitative synthesis. The characteristics and principal findings of the included studies are presented in Table I.

The included studies reported a broad range of cardiovascular outcomes, reflecting differences in lymphoma subtype, treatment exposure,age at treatment, follow-up duration, and outcome definitions. Across the evidence base, cardiovascular complications included cardiomyopathy, ventricular dysfunction, arrhythmias, coronary artery disease, valvular abnormalities, pericardial disease, and vascular complications. In a large retrospective cohort, Armenian et al. reported a higher incidence of cardiac complications among survivors of NHL than among noncancer controls (10). Other studies of long-term survivors demonstrated clinically important coronary and valvular disease following mediastinal radiotherapy (12, 28–30, 44). These findings indicate that cardiovascular risk may persist well beyond completion of lymphoma therapy.

The pattern of cardiovascular complications also varied according to lymphoma subtype and treatment exposure. Direct cardiovascular involvement may occur in patients with mediastinal or other thoracic disease, whereas treatment-related injury is particularly relevant after anthracycline exposure and mediastinal radiotherapy. Because the included studies differed substantially in populations and endpoints, prevalence estimates should be interpreted cautiously rather than considered directly comparable across studies.

Chemotherapy-Induced Cardiotoxicity in Pediatric Lymphoma

Cardiotoxicity associated with childhood cancer treatment can be categorized as acute, early-onset, or late-onset (15). Chemotherapy-related cardiovascular injury may present as ventricular dysfunction, cardiomyopathy, arrhythmias, hypertension, acute coronary syndromes, or thromboembolic complications (17–20). Anthracyclines are among the agents most strongly associated with cardiotoxicity. Other potentially cardiotoxic therapies include alkylating agents such as cyclophosphamide and selected targeted therapies (17–20).

Anthracycline-associated cardiotoxicity has been linked to oxidative stress, lipid peroxidation, apoptosis, necrosis, and alterations in cardiac proteins and transcriptional pathways (21). Clinically, anthracycline exposure may lead to dilated cardiomyopathy and impaired systolic function (22). Changes in echocardiographic indices before and after anthracycline-based therapy also support the importance of detecting subclinical myocardial dysfunction before overt heart failure develops (23).

Strategies to reduce anthracycline-associated cardiotoxicity are therefore clinically important. Studies included in this review reported cardioprotective effects of dexrazoxane in children and young adult survivors exposed to doxorubicin, including evidence of preserved long-term cardiac function without an apparent compromise in antitumor efficacy (24–26). These findings support the consideration of cardioprotective strategies in patients receiving

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anthracycline-based treatment, particularly those at higher cardiovascular risk.

Cyclophosphamide is also associated with cardiac toxicity, including rare but potentially severe myocarditis and myocardial injury (27). However, the evidence specifically addressing cyclophosphamide-related cardiovascular toxicity in pediatric lymphoma is limited. This gap highlights the need for prospective studies that evaluate the cardiovascular effects of individual agents within contemporary combination regimens.

Radiotherapy-Induced Cardiovascular Complications

Radiotherapy, particularly when the heart and mediastinal structures receive substantial exposure, may cause chronic pericardial disease, premature coronary artery disease, atherosclerosis, cardiomyopathy, valvular disease, and conduction abnormalities (28). These complications may become clinically apparent years or decades after treatment. In childhood cancer survivors, cardiovascular abnormalities have been reported even among patients who did not receive cardiotoxic chemotherapy, emphasizing the importance of radiation exposure as an independent contributor to long-term cardiovascular risk (29). Studies of Hodgkin lymphoma survivors treated with mediastinal radiotherapy reported structural, valvular, and conduction abnormalities, as well as impaired exercise capacity (30). Similarly, long-term cohort studies have demonstrated increased risks of coronary artery disease and myocardial infarction after treatment for Hodgkin lymphoma (28, 44).

Mechanisms Underlying Cardiovascular Complications in Pediatric Lymphoma

Lymphoma may directly involve the cardiovascular system and cause structural or functional abnormalities. Tumor infiltration can affect the myocardium, pericardium, endocardium, or blood vessels and may present as cardiac masses, pericardial effusion, myocardial infiltration, or vascular compression (31–33). Primary cardiac lymphoma is uncommon but may cause heart failure, arrhythmias, or cardiac tamponade and therefore requires prompt diagnosis and treatment (32, 33).

Mediastinal or thoracic lymphoma may compress cardiac structures and the great vessels, resulting in pericardial effusion, vascular obstruction, and hemodynamic compromise (34, 35). In advanced disease, systemic inflammation, constitutional symptoms, and reduced functional capacity may further increase cardiovascular stress (36).

Inflammatory and immune-mediated mechanisms may also contribute to cardiovascular complications. Cytokine release, systemic inflammation, endothelial dysfunction, vasculitis, and thrombotic processes may increase cardiovascular risk (37, 38). These mechanisms may coexist with direct tumor involvement and treatment-related injury, making it difficult to attribute an individual cardiovascular event to a single cause.

Clinical Manifestations of Cardiovascular Complications in Pediatric Lymphoma

Cardiovascular complications range from asymptomatic or clinically mild abnormalities to life-threatening conditions such as cardiac tamponade and heart failure (39, 40). Pericardial effusion may present with chest pain, dyspnea, cough, or orthopnea, whereas myocardial dysfunction may manifest as fatigue, exercise intolerance, or clinical features of heart failure (41, 42).

Arrhythmias, including tachycardia, bradycardia, and palpitations, may result from direct cardiac involvement or treatment-related toxicity. Vascular compression syndromes may cause facial swelling, dyspnea, and hemodynamic instability (43, 44). Early recognition can be challenging because these symptoms overlap with manifestations of lymphoma, infection, anemia, and treatment toxicity. A structured cardiovascular assessment is therefore particularly important in patients with known cardiac risk factors or concerning symptoms.

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Diagnostic Approaches for Cardiovascular Complications in Pediatric Lymphoma

Echocardiography is a central noninvasive modality for evaluating cardiac structure and function, including ventricular function, pericardial effusion, valvular abnormalities, and intracardiac masses (47). Cardiac magnetic resonance imaging (MRI) provides detailed assessment of myocardial tissue characteristics, cardiac masses, pericardial involvement, myocardial strain, and perfusion (48–50). Computed tomography (CT) angiography can evaluate vascular involvement and compression and define the extent of mediastinal or thoracic disease (51, 52). Positron emission tomography combined with CT (PET/CT) can identify metabolically active lymphoma involving the heart, mediastinum, and other extranodal sites and can support staging and treatment-response assessment (53, 54).

Cardiac biomarkers, including troponin, B-type natriuretic peptide (BNP), and N-terminal pro-BNP (NT-proBNP), may provide additional information regarding myocardial injury and cardiac dysfunction. Serial assessment may assist with longitudinal monitoring in selected high-risk patients (5). Electrocardiography can identify arrhythmias, conduction abnormalities, and ischemic changes and remains an important component of cardiovascular assessment (47).

In selected patients with suspected cardiac involvement, endomyocardial biopsy may provide histopathological confirmation of lymphoma infiltration or myocarditis and may help guide treatment (48). Overall, a multimodal approach combining clinical assessment, biomarkers, electrocardiography, echocardiography, advanced imaging, and, when indicated, tissue diagnosis can facilitate timely identification and management of cardiovascular complications.

Management Strategies for Cardiovascular Complications in Pediatric Lymphoma

Management requires close collaboration among pediatric oncologists, cardiologists, and other relevant specialists. Multidisciplinary decision-making is particularly important when cardiovascular toxicity affects the choice or intensity of cancer therapy (55, 56). Management of heart failure may include angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, and selected inotropic agents, according to clinical severity (57). Antiarrhythmic therapy may be required for clinically significant rhythm disturbances (58, 59). Symptomatic pericardial effusion or cardiac tamponade may require pericardiocentesis, while selected patients with structural cardiac masses, thrombi, or vascular obstruction may require surgical or interventional procedures (60–64). Prevention and early detection remain preferable to management of advanced cardiac dysfunction; therefore, baseline risk assessment and longitudinal surveillance should be incorporated into survivorship care.

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Table I: Characteristics and cardiovascular findings of studies included in the systematic review

Author	Year	Key findings	Population	Number of participants	Study type	Reference(s)
Chow EJ., et al.	2023	In a cohort of young adult survivors of childhood cancer, dexrazoxane demonstrated a cardioprotective effect nearly two decades following their initial exposure to anthracycline chemotherapy.	children with acute lymphoblastic leukemia or Hodgkin lymphoma, who received doxorubicin with or without dexrazoxane	195	Randomized clinical trial	25
Olivieri J,. Et al.	2017	Doxorubicin substitution with nonpegylated liposomal doxorubicin may be profitable in lymphoma patients at high risk for AC-induced cardiotoxicity because it prevented the excess of cardiac toxicity expected while preserving the antitumor efficacy.	lymphoma patients undergoing first-line treatment with conventional or liposomal Anthracyclines	99	prospective observational trial	26
Materazzo C., et al.	2017	long-term cardiac complications are prevalent in individuals who have undergone treatment for Hodgkin Lymphoma Survival (HLS) using the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen combined with radiotherapy. The most frequently observed complications within this cohort were primarily coronary artery disease and valvular abnormalities.	Hodgkin Disease Survivors	53	Retrospective cohort study	47
Armenian SH., et al.	2016	Incidence rate ratio (IRR) of cardiac complications among survivors of non-Hodgkin lymphoma was significantly higher when compared with noncancer controls (IRR=1.41)	survivors of childhood and young adult cancers	36232(cancer) 73545(Control)	Retrospective cohort study	10
Asselin BL., et al.	2016	Dexrazoxane demonstrated cardioprotective effects without compromising antitumor efficacy. Additionally, it did not lead to an increase in the incidence of toxicities and was not associated with a statistically significant rise in the occurrence of secondary malignancies within the context of this doxorubicin-based chemotherapy regimen.	Patients Treated for T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma	537	Randomized clinical trial	23
Lipshultz SE., et al.	2012	Survivors of childhood cancer who have not undergone cardiotoxic therapies still exhibit cardiovascular abnormalities, systemic inflammation, and an elevated risk of developing atherosclerotic disease.	Childhood cancer survivors(Leukemia-Lymphoma-Embryonal-Sarcoma)	201 survivors of childhood cancer(39 lymphoma survivors)	Retrospective cohort study	29
Swerdlow AJ., et al	2007	The risk of death from myocardial infarction after treatment for Hodgkin disease remains high for at least 25 years.	Hodgkin Disease Survivors	7033	Retrospective cohort study	44

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Adams MJ., et al.	2004	A diverse range of clinically significant cardiovascular abnormalities is prevalent among long-term survivors of Hodgkin's disease who received mediastinal irradiation at a young age.	Hodgkin Disease Survivors	48	Retrospective cohort study	30
Hull MC., et al.	2003	In the context of radiation therapy for Hodgkin lymphoma, there are statistically elevated rates of valve surgery and coronary revascularization procedures anticipated over the subsequent 10 to 20 years. Additionally, the incidence of coronary vascular disease correlates with higher radiation doses as well as traditional risk factors associated with coronary heart disease.	Non-Hodgkin lymphoma survivors whom received radiotherapy	404	Retrospective cohort study	12
Felker GM., et al.	2000	Patients with cardiomyopathy due to doxorubicin therapy have an especially poor prognosis.	Patients with cardiomyopathy	1230	Retrospective cohort study	16
Boivin JF., et al.	1992	Radiation therapy to the mediastinum increases the risk of coronary artery disease	Patients treated for Hodgkin's disease.	4665	Retrospective cohort study	28

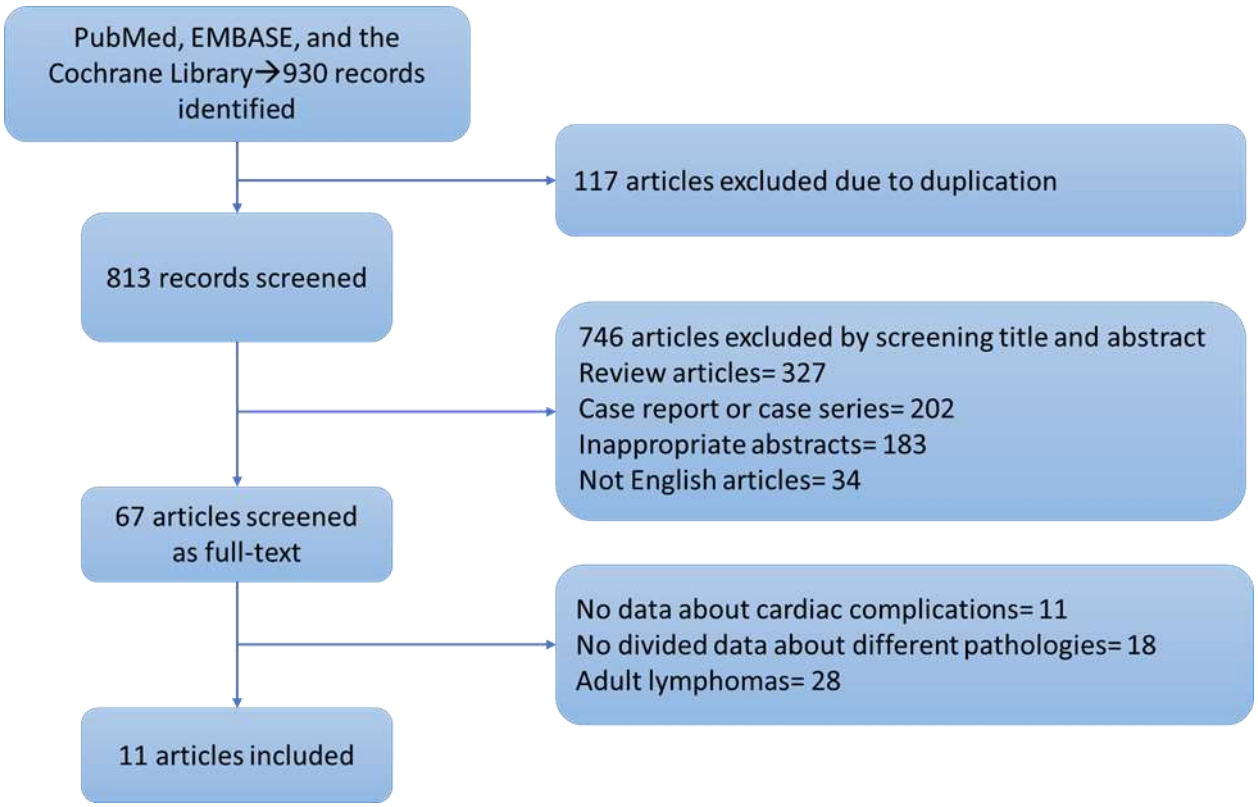

Figure 1. PRISMA flow diagram showing the identification, screening, eligibility assessment, and inclusion of studies in the systematic review.

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Discussion

This systematic review identified 11 studies evaluating cardiovascular complications in pediatric lymphoma and childhood cancer survivors with lymphoma. Although the evidence was heterogeneous, several consistent patterns emerged. First, cardiovascular risk extends beyond the period of active lymphoma treatment. Second, the nature of cardiovascular injury differs according to treatment exposure: anthracyclines are strongly associated with myocardial dysfunction and cardiomyopathy, whereas mediastinal radiotherapy is particularly associated with coronary, valvular, pericardial, and conduction abnormalities. Third, direct lymphoma involvement can produce acute cardiovascular complications that are mechanistically distinct from treatment-related toxicity.

The chemotherapy-related findings are consistent with the long-term clinical concern surrounding cumulative anthracycline exposure. The included studies evaluating dexrazoxane provide an important comparison between conventional anthracycline treatment and cardioprotective strategies. Asselin et al. reported cardioprotection without compromising antitumor efficacy, while Chow et al. demonstrated a cardioprotective effect that remained evident nearly two decades after anthracycline exposure (23, 25). Olivieri et al. further reported low cardiotoxicity with substitution by nonpegylated liposomal doxorubicin in patients considered at higher risk (26). Taken together, these studies suggest that cardiotoxicity prevention can be incorporated into lymphoma treatment without necessarily reducing oncologic effectiveness. However, the differences in study design, patient populations, and treatment protocols limit direct comparison and prevent definitive conclusions about which strategy is optimal for all patients.

The radiotherapy literature demonstrates a different pattern of late cardiovascular injury. Studies of Hodgkin lymphoma survivors treated with mediastinal irradiation reported substantial burdens of coronary artery disease, valvular abnormalities, conduction defects, and impaired cardiac performance (28–30, 44). In contrast to anthracycline cardiotoxicity, which may be detected during or soon after treatment, radiation-associated complications may emerge many years later. This difference has important implications for survivorship programs: a patient who completes therapy without early cardiac symptoms should not necessarily be considered free of cardiovascular risk.

The studies also differ in the cardiovascular outcomes they emphasize. Some focus on clinically overt events such as heart failure or myocardial infarction, whereas others identify subclinical structural or functional abnormalities. This variation likely contributes to the wide range of reported complication rates and makes pooled prevalence estimates inappropriate. The evidence therefore supports a risk-adapted surveillance model rather than a single uniform follow-up schedule. Patients with higher cumulative anthracycline exposure, mediastinal radiation, pre-existing cardiovascular risk factors, or early evidence of cardiac dysfunction may require more intensive follow-up.

The review also highlights an important evidence gap. Most available studies are retrospective or observational, many include mixed childhood cancer populations, and treatment regimens vary considerably across decades. Consequently, evidence derived from older treatment protocols may not fully represent current pediatric lymphoma therapy. Prospective, lymphoma-specific cohorts using standardized cardiovascular endpoints and contemporary treatment exposures are needed to determine the incidence, predictors, and reversibility of cardiovascular injury. Future studies should also distinguish symptomatic events from subclinical abnormalities and report cumulative treatment exposures in sufficient detail to support risk stratification.

Study Limitations

The main limitations of this review are the small number of eligible studies, heterogeneity in study designs and populations, variation in cardiovascular outcome definitions, and

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differences in treatment regimens and follow-up duration. These factors prevented quantitative pooling and limit direct comparison between studies. In addition, restricting eligibility to English-language publications may have introduced language bias.

Conclusion

This systematic review underscores the clinical importance of cardiovascular complications associated with lymphoma and its treatment in children and adolescents. Anthracycline exposure and mediastinal radiotherapy are particularly important determinants of long-term cardiovascular risk, while direct cardiac involvement may produce acute complications. Standardized, risk-adapted cardiovascular assessment during treatment and long-term survivorship follow-up is needed. Future prospective studies should evaluate contemporary treatment regimens and establish evidence-based surveillance strategies for pediatric lymphoma survivors.

Availability of Data

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare that they have no relevant financial or non-financial interests to disclose.

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Ethical Considerations

This systematic review used data from previously published studies and did not involve human participants, identifiable personal data, or animal experiments. Therefore, institutional ethics approval and informed consent were not required.

Authors' Contributions

ME and GMH independently conducted the literature search, study selection, data extraction, and methodological quality assessment. All authors contributed to the interpretation of the findings and the preparation or critical revision of the manuscript. All authors read and approved the final manuscript and agree to be accountable for the work.

Artificial Intelligence Use Disclosure Statement

The authors declare that no generative artificial intelligence or AI-assisted technologies were used in the preparation, writing, editing, analysis, or interpretation of this manuscript.

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