META-ANALYSIS

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Ocular involvement in newly diagnosed pediatric leukemia: A systematic review and meta-analysis

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ABSTRACT

Importance: Ocular involvement in pediatric leukemia is often underrecognized, especially in asymptomatic cases. Prevalence estimates of childhood leukemic ophthalmopathy range from 0.32% to 71%, depending on the study design and population.

Objective: To determine the prevalence and describe the nature of ocular involvement in newly diagnosed pediatric leukemia through systematic review and meta-analysis.

Methods: A comprehensive search of MEDLINE, Embase, Cochrane, and Web of Science databases was conducted up to July 2024. Studies reporting on ocular involvement at diagnosis in children aged 18 years or younger with leukemia were included. Cases of relapsed disease were excluded as were those receiving concurrent treatment. A random effects meta-analysis using an inverse-variance restricted maximum likelihood approach was performed for prevalence estimates.

Results: Fourteen studies involving 2989 pediatric leukemia patients were included. The overall pooled prevalence of ocular involvement at diagnosis was 20.32% (95%CI = 9.88%–33.08%). The prevalence of asymptomatic ocular involvement was higher at 23.90% (95%CI = 10.27%–40.63%) compared to 14.75% (95%CI = 0.00%–45.31%) for symptomatic involvement alone. High heterogeneity (I^2 = 97.7%) was observed across studies, likely driven by differences in study design and populations.

Interpretation: Ocular involvement in newly diagnosed pediatric leukemia is more common than previously understood, particularly for asymptomatic cases. Current practices of selective ophthalmic assessment may miss a number of early-stage ocular manifestations, emphasizing the need for all newly diagnosed patients to be screened for ophthalmic involvement at the time of diagnosis.

KEYWORDS

Adolescent, Child, Leukemia, Oncology, Ophthalmology

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INTRODUCTION

Leukemia is the most common malignancy of childhood and adolescence accounting for nearly 25% of all cancers diagnosed in those aged less than 20 years. The age-adjusted incidence of leukemia in the United States is 4.9 per 100 000 children and adolescents every year.[1] The leukemias are a heterogeneous group of malignant neoplasms of hematopoietic stem cells, characterized by diffuse proliferation of clonal cells in the bone marrow.[2] This uncontrolled proliferation causes widespread replacement of functional hematopoietic cells, ultimately leading to symptomatic disease.[3,4]

Extramedullary leukemic involvement in children typically involves the musculoskeletal, renal, hepatic, and ocular systems.[5,6] Leukemic ophthalmopathy can be classified as either primary (i.e., direct) or secondary (i.e., indirect) involvement.[3,7,8] Primary involvement results from direct infiltration of leukemic cells into the orbit, anterior, and posterior segments including the iris, choroid, and retina.[7,8] Leukemic retinopathy, first described by Liebreich in 1861, refers to the intraretinal hemorrhages (IRH), white-centered hemorrhages (WCH), and cotton-wool spots (CWS) observed in leukemic patients on fundoscopy.[9] Leukemic cells can also infiltrate neuro-ophthalmic structures causing optic disc edema, papilledema, and other cranial nerve III, IV, and VI palsies,[3,7] although almost every ocular structure has the potential to be implicated.[10–12] Secondary ocular involvement is caused by the hematologic dysfunction characteristic of the disease including anemia, thrombocytopenia, blood hyperviscosity, and immunosuppression which can manifest as retinal and vitreous hemorrhages, ischemia, and opportunistic ocular infections.[3,7]

Intraocular manifestations of leukemia are readily recognized as being present at the time of diagnosis, however, the prevalence and nature of ophthalmic involvement can vary depending on the disease subtype and time point in the natural history.[12–17] The retina is the most commonly infiltrated ocular tissue in early-stage leukemia.[11,18,19] However, it has been suggested up to 90% of patients across all ages will develop leukemic retinopathy at some point throughout the disease.[20] Further, the degree of symptomatic ocular involvement at diagnosis can vary, with most patients presenting with asymptomatic disease.[21]

The objective of this systematic review and meta-analysis was to describe and quantify the prevalence of ocular involvement in newly diagnosed cases of childhood leukemia. To the authors' knowledge, no systematic review consolidating this literature has been carried out to date. This research question is of clinical relevance as no ophthalmic screening guideline currently exists for children and adolescents newly diagnosed with leukemia. A better understanding of the frequency of ophthalmic involvement in this group is a necessary first step toward refining best practices for screening and management of the ocular manifestations of this disease.

METHODS

This study follows Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, [22,23] and is registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024548493). Research ethics board approval was not required as this study uses previously published and de-identified data.

Eligibility criteria

The inclusion criteria for this review were as follows: (1) primary research (e.g., randomized trials, case-control studies, cohort studies, cross-sectional studies, clinical trials); (2) newly diagnosed cases of leukemia in those aged 18 years of age and younger; (3) ocular involvement at the time of diagnosis. Ocular involvement was defined as all primary and secondary ocular, orbital, or neuro-ophthalmic signs and symptoms owing to leukemia. Ocular involvement secondary to iatrogenic complications of leukemia (i.e., chemotherapy and irradiation) was excluded. In instances where it was unclear whether the ocular involvement was due to leukemia or its treatment, this source was excluded. For studies reporting data on both adults and children, data pertaining to the child cohort was extracted.

Gray literature, abstracts, reviews, case reports, case series, and non-English sources were excluded. Studies reporting on patients with a history of leukemia, other malignancy, or any current or historic use of chemotherapy or radiation were excluded. Studies were not excluded based on leukemic subtype, ocular or systemic comorbidities, and medication history other than those stated above.

Information sources

A comprehensive search was conducted across four electronic databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Web of Science. Searches were carried out in each database on July 29, 2024. All articles published from inception to this date were assessed for inclusion. The reference lists of all included studies were reviewed by Kristina Nazzicone and Rachel Kim to obtain additional eligible articles.

Search strategy

A search strategy was created in collaboration with a Health Sciences Librarian at Queen's University. Literature searches used both controlled vocabulary terms and synonymous free-text words to capture articles related to

leukemia or 'hematologic malignancy', pediatrics, childhood or adolescence, ocular, systemic or extramedullary involvement, manifestations, or signs/symptoms. Supporting Information 1 outlines the complete search strategy for each database.

Selection and data collection process

Search results were exported from each database and uploaded to Covidence where duplicates were either automatically removed by Covidence or manually removed by reviewers at the first stage of screening. Potential sources of evidence were independently screened in duplicate by two reviewers (Kristina Nazzicone and Rachel Kim) at both title and abstract, and full-text levels. Title, abstract, and full-text screening were guided by a standardized resource distributed to reviewers in advance of starting the screening process. Conflicts were resolved independently by a third reviewer (Alexa Fine or Aidan Pucchio). Data extraction was performed using Microsoft Excel by one independent reviewer (Kristina Nazzicone), with 10% of the extractions verified by a second reviewer (Rachel Kim) to ensure extractor agreement.

Data items

Descriptive patient and study information was extracted from each included source of evidence which included first author name, publication year, journal title, years and country of data collection, study setting, and design. Participant data including age, sex, gender, ethnicity, comorbid ocular and systemic diagnoses, leukemia subtype, severity, method of diagnosis, and associated signs and symptoms were also extracted, whenever possible.

The sample size, event frequency, and description of ophthalmic involvement were extracted as outcome data. Data pertaining to time from diagnosis to ocular assessment, description of ocular examination, whether the ocular involvement data was pre-specified by the study team prior to data collection, and whether ocular involvement was limited to symptomatic ocular manifestations was determined. Studies characterized as having carried out full ophthalmic examination included three or more of the following components: visual acuity testing, slit-lamp biomicroscopic examination (or alternative anterior segment assessment), intraocular pressure (IOP) measurement or dilated fundus examination using direct and/or indirect ophthalmoscopy. To be placed in the 'asymptomatic' category, studies must have either assessed patients for asymptomatic ophthalmic manifestations alone or alongside any overt/symptomatic manifestations of the disease.

Study risk of bias assessment

The methodological risk of bias (RoB) was assessed for each study using the Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies.[24] Assessments were made by a single reviewer (Rachel Kim) with 10% verified by a second reviewer (Kristina Nazzicone) to ensure agreement. Articles with $< 49\%$ of questions scored as "yes" were classified as having high RoB, 50%–79% as moderate risk, and $> 80\%$ as low RoB.[25,26] Findings from the RoB assessment were described narratively and studies were not excluded on the basis of quality.

Effect measures

Continuous variables are displayed as mean and standard deviation or proportions, where applicable, and categorical variables are presented as absolute and relative frequencies.[27] In cases where range, median, or interquartile range was reported, methods published by Wan and colleagues for estimating mean and standard deviation were used.[28] Cochrane's formula for combining means into a single group was used in instances where means were presented for different subgroups separately.[29] In instances where more than one source appeared to refer to the same set of participants, the study with the larger total sample size was included if corresponding authors could not be contacted.

Data synthesis and analysis methods

The metaprop function within the "meta" package in R Statistics 4.4.0 (The R Foundation) was used to calculate individual and weighted pooled prevalence estimates along with corresponding 95% confidence intervals (CIs) for meta-analyses.[30,31] A random-effects meta-analysis was performed using an inverse-variance restricted maximum-likelihood approach to estimate between-study variance (τ^2). The Q-profile method was used for CI of τ^2 and τ. Data was transformed using the Freeman-Tukey double arcsine transformation. CIs were estimated using the Clopper-Pearson method and the Hartung-Knapp-Sidik-Jonkman distribution.[32–35] The metareg function within the "meta" package in R statistics was used to perform a simple meta-regression using possible effect modifiers with sufficient data.

The presence of statistical heterogeneity was assessed through visual inspection of forest plots, Cochrane's Q test (chi-squared), and Higgins I^2 statistic.[36] The presence of publication bias was assessed using a funnel plot and Egger's test for qualitative and quantitative assessment, respectively.

RESULTS

Study selection

A total of 2875 references were identified through database search with 2213 unique studies remaining after duplicate removal. Title and abstract screening yielded 484 potentially eligible studies intended to be screened at the full-text level. Twenty-one full-text manuscripts could not be retrieved, yielding 463 studies able to be assessed for eligibility. Four hundred and forty-nine studies were ultimately deemed ineligible primarily due to incorrect study design ($n = 166$), patient population ($n = 110$), or language ($n = 96$). Fourteen studies were ultimately included in the present study (Figure 1).

Study characteristics

Included studies were published from 1989 to 2022 with data collection spanning from 1963 to 2021. Study designs included eight prospective (57.1%) and six retrospective (42.9%) cohort studies. Country of data collection included Turkey (21.4%), India (21.4%), United States (14.3%), Malaysia (14.3%), Saudi Arabia (7.1%), Israel (7.1%), Ethiopia (7.1%) and a combination of Sweden, Denmark, and Finland (7.1%). All but one study (92.9%) collected data from hospitals, while one study (7.1%) used data from an acute lymphocytic leukemia (ALL) registry. Four studies solely reported data on acute lymphoblastic leukemia (ALL; 28.6%) and another four reported data on the two acute leukemia subtypes together (ALL and acute myeloid leukemia [AML]; 28.6%). Three studies (21.4%) reported data on a mixed cohort of acute and chronic myeloid and lymphoid subtypes. Two studies reported data on acute myelomonocytic leukemia (AMML; 12.3%) and a single study reported data on a cohort of AML patients (7.1%). A complete list of study characteristics is included in Table S1.

Definitions and methods of diagnosing ocular involvement varied across included studies. For instance, only half of the dataset (seven studies; 50.0%) performed a full ocular examination, whereas the other half either performed selective aspects of the exam (e.g., IOP measurement) or only assessed symptomatic or overt findings (seven studies; 50.0%). In studies where a full ophthalmic examination was not performed, all but one pre-specified which ocular manifestation would be assessed for involvement and only performed the necessary diagnostic tests for that manifestation (six studies; 85.7%). In studies, pre specifying ophthalmic manifestations prior to assessment, ophthalmic involvement included: proptosis, elevated IOP, "neurological symptoms", "signs and symptoms of chloroma/orbital granulocytic sarcoma (OGS)", and specific retinal findings. Studies were classified according to whether or not ocular involvement was symptomatic or asymptomatic. In general, studies reporting symptomatic involvement were more likely to have pre-specified ocular manifestations and less likely to have completed a full ophthalmic examination. The majority of studies assessing asymptomatic ophthalmic involvement performed a complete ophthalmic examination (seven studies; 77.8%). Details pertaining to the ways ophthalmic involvement is defined and assessed for each included study are outlined in Table S2.

Individual study RoB

In general, included studies were successful in controlling for RoB. Of the 14 included cohort studies, 12 (85.7%) were of low risk and two (14.3%) were of moderate RoB (Figure S1). Thirteen (92.8%) studies used an appropriate sample frame, while one (7.1%) was unclear for this domain. While all 14 studies exhibited appropriate sampling methods, only nine (64.3%) studies had adequate sample sizes. Four (28.6%) studies had inadequate sample sizes, and one (7.1%) study was unclear, introducing the potential for type II errors. Thirteen (92.8%) studies explained the study setting and subjects thoroughly, and five were unclear about their methods of statistical analysis (35.7%). All studies described standardized measurement and diagnostic criteria and reported no loss to follow-up.

Describing ocular involvement

Both primary and secondary ophthalmic manifestations were reported in the included studies in this review. IRH was the most frequently described manifestation, affecting 62 patients across five studies. Other common retinal findings included WCH noted in 19 patients across four studies, subhyaloid hemorrhages in 13 patients across two studies, CWS in six patients across two studies, and macular hemorrhage in two cases in a single study. One or more of these retinal findings was noted in four patients across two studies, however specifics were not provided. Dilated and tortuous retinal veins were reported in 15 patients across two studies, along with less frequent occurrences of vitreous hemorrhage (two patients; two studies) and retinal vascular sheathing in one patient.

Neuro-ophthalmic signs included papilledema, observed in 13 patients across four studies, and "optic disc edema" in four patients in a single study. A 6th nerve palsy was observed in three patients in two studies and Horner syndrome in two patients from the same study. Five patients across two studies described visual acuity abnormalities. Three patients from the same study cohort experienced diplopia.

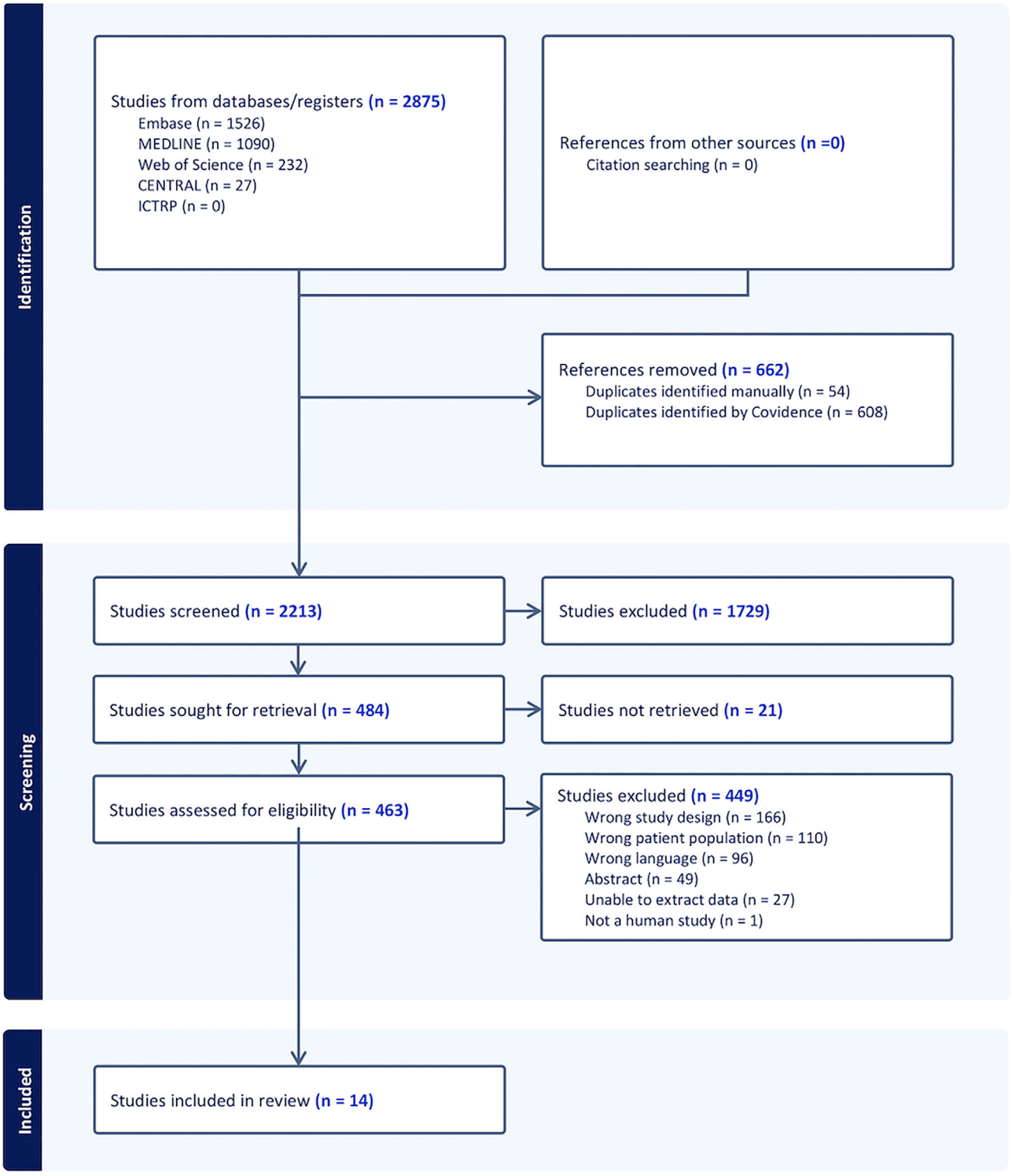

FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flowchart of included studies exported from Covidence.

Ocular infiltration was also observed in the choroid and conjunctiva. Choroidal infiltration, resulting in exudative retinal detachment, was noted in three cases across two studies and conjunctival infiltration was noted in another. One study broadly described "leukemic infiltrates" in a single patient, without specifying which ocular tissue(s) were affected. Painless proptosis and other manifestations caused by OGS were observed in five patients across two studies.

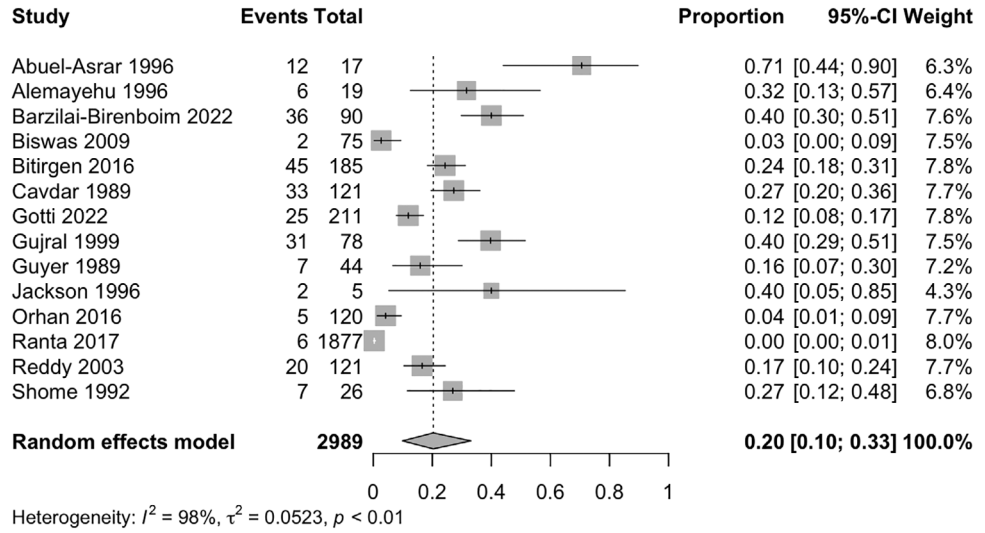

FIGURE 2 Forest plot of the meta-analysis of ocular involvement in newly diagnosed pediatric cases of leukemia. Events represent the number of individuals with ophthalmic involvement.

Exophthalmos was reported in 42 patients across five studies. In one of these patients, ocular proptosis was due to retrobulbar hemorrhage. Other notable anterior segment findings included subconjunctival hemorrhage in six patients across two studies and conjunctival vessel dilation in two patients in the same study cohort. Chemosis was seen in two patients in different cohorts. Three patients experienced preseptal cellulitis and another 36 experienced increased ocular pressure, both in a single study. Finally, one patient each was observed to have keratomalacia, exposure keratitis, ptosis, and lagophthalmos (Table S2).

Results of syntheses

Meta-analyses revealed high inter-study heterogeneity (I^2 = 97.7%, 95%CI = 97.1%–98.2%; τ^2 = 0.0523, 95%CI = 0.0248–0.1465), therefore a random-effects model was used. The prevalence of ocular involvement in newly diagnosed cases of pediatric leukemia across all subtypes (n = 2989) was found to be 20.32% (95%CI = 9.88%–33.08%; Figure 2). The prevalence of symptomatic ocular involvement at diagnosis was determined to be 14.75% (95%CI = 0.00%–45.31%), whereas studies reporting either asymptomatic manifestations alone or in combination with symptomatic involvement resulted in a prevalence of 23.90% (95%CI = 10.27%–40.63%; Figure S2).

Simple meta-regression was performed for variables that included the complete dataset (k = 14). Study design explained 2.64% of inter-study heterogeneity and was not found to significantly influence prevalence (QM (1) = 1.5542, P = 0.2363, R^2 = 2.64%). The country of data collection explained 29.37% of inter-study heterogeneity and was not found to significantly influence prevalence (QM (7) = 1.7453, P = 0.2572, R^2 = 29.37%). The year of publication explained 11.49% of inter-study heterogeneity and was not found to significantly influence prevalence (QM (1) = 2.7157, P = 0.1253, R^2 = 11.49%). The leukemia subtype explained 0.00% of inter-study heterogeneity and was not found to significantly influence prevalence (QM (4) = 0.3500, P = 0.8378, R^2 = 0.00%). Full examination status explained 0.00% of inter-study heterogeneity and was not found to significantly influence prevalence (QM (1) = 0.0174, P = 0.8973, R^2 = 0.00%).

Sensitivity analyses

Sensitivity analysis was conducted to assess the existence of outliers contributing to extreme results. Influence analysis revealed one study (Ranta 2017) contributed significantly to inter-study heterogeneity. Removing this study from meta-analyses did not substantially alter results for overall prevalence (n = 1112; 23.09% (95%CI = 12.76%–35.21%); Figure S3).

Reporting biases

Egger's test was significant (t (4.97) = 7.9656, P = 0.0003) suggesting funnel plot asymmetry (Figure 3). Adjusted funnel plot using the Trim and Fill method was not significant (t (0.95) = 2.1977, P = 0.3557), suggesting asymmetry might be due to publication bias (Figure S4).

DISCUSSION

This systematic review and meta-analysis consolidates the limited primary data that exists reporting the prevalence of ophthalmic involvement in newly diagnosed cases of

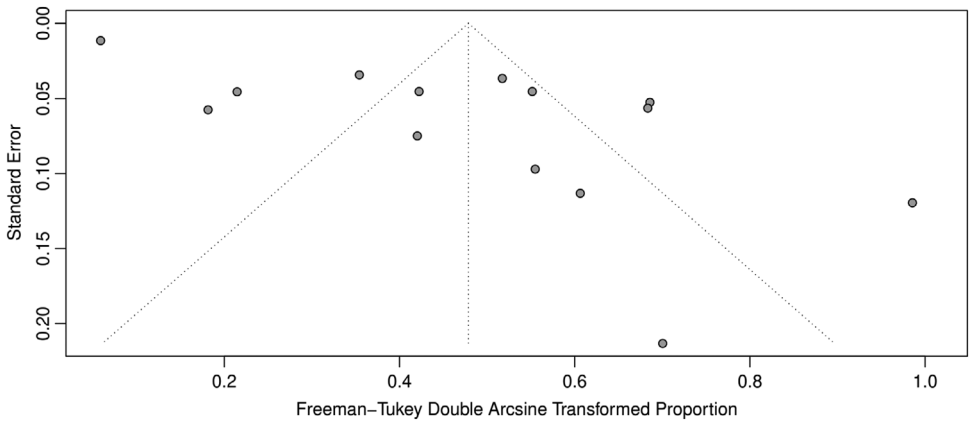

FIGURE 3 Funnel plot of all included studies.

childhood leukemia. Through meta-analyses of 14 studies and 2989 patients, the overall prevalence of ocular involvement in newly diagnosed leukemia was found to be 20.32%. Subgroup meta-analyses to assess the prevalence of ocular involvement in studies reporting asymptomatic ocular involvement yield a slightly higher prevalence of 23.90% compared to 14.75% in studies only assessing for overt or symptomatic ocular involvement. This distinction is important as most patients will not present with overt ocular signs and symptoms at the time of initial diagnosis.

Prior to this review, knowledge of the frequency of ophthalmic involvement in pediatric leukemia was limited to isolated accounts in primary research studies and occasionally extrapolated from data in mixed cohorts of adults and children.[37,38] In general, ophthalmic involvement in younger patients has been shown to be less prevalent than in their adult counterparts. For instance, work by Karesh and colleagues estimates the prevalence of leukemic retinopathy in adults to be upwards of 53%.[18] In another study, the prevalence of IRH, CWS, and WCH in a cohort of both children and adults yielded a lower estimate of approximately 43%.[9] These differences highlight the need for further inquiry in pediatric populations.

Prevalence estimates of ophthalmic involvement in cohorts of newly diagnosed leukemia in children and youth are also variable, ranging from 0.32%–71% in the present study.[39,40] This might be explained in large part by heterogeneous study designs and sample populations.[19] For instance, although this review aimed to quantify ocular involvement in newly diagnosed cases of leukemia, patient presentations of 'newly diagnosed' disease were highly variable. Disease severity at the initial presentation of leukemia can vary widely depending on geographical location and is strongly linked to the social determinants of health. Patients living in under-resourced countries are more likely to present at a later stage compared to those in more developed nations.[41] Newly diagnosed disease, therefore, still comprises a heterogeneous group of patients presenting at varied points in the natural history of the disease. This is relevant to note as the presence and extent of ocular involvement can vary depending on disease severity,[12–17] suggesting global prevalence estimates are unlikely to be generalizable to all pediatric cohorts.

This review sought to quantify the overall prevalence of ocular involvement in pediatric leukemia as well as the prevalence of various individual ocular findings. Given the limited availability of primary data, those planned analyses were not carried out. Instead, subgroup meta-analyses were performed for studies reporting asymptomatic ocular involvement separately. This decision was driven by the consensus that overt ophthalmic manifestations, such as exophthalmos and palpebral edema, are rare presenting signs of *de novo* disease.[19,21] Results of these analyses suggest full ocular examination to assess all asymptomatic involvement yields a higher prevalence than identified in studies assessing for symptomatic manifestations alone (23.90% vs. 14.75%). The understanding that children are likely to present with asymptomatic involvement at diagnosis has been highlighted in other research on this topic.[10,42] This brings up the consideration that ocular screening at the time of diagnosis might be underutilized, regardless of whether patients endorse ocular symptoms or show any overt signs of involvement.

Ophthalmic exams at the time of diagnosis are carried out in a small handful of centers across European countries and the United States.[9,43,44] However, no guideline emphasizing the importance of screening in this group currently exists in Canada. Guidelines emphasizing the importance of screening at diagnosis and routinely thereafter following a diagnosis of pediatric type 2 diabetes (T2D) are accepted and endorsed by experts in this area.[45] Recent estimates

TABLE 1 Sample screening questions for children and guardians to assess leukemic optic involvement at diagnosis

Category	Questions
Vision changes - *might indicate retinopathy, optic nerve edema, retinal detachment*	• Have you noticed things are blurry or fuzzy, or it is hard to see clearly sometimes? • Are there parts of what you see that look like they're missing or covered by a shadow? • Do you ever feel like you are seeing two of everything (double vision), especially when you look around in different directions? • Do you ever notice black/gray dots, blobs or sparkles, and lightning streaks in your eyes?
Eye appearance - *might indicate proptosis, EOM infiltration, chloroma/OGS*	• Have you ever noticed one or both of your eyes are sticking out more than usual? • Do you feel like it is hard to close your eyes all the way, or do you feel like they do not close properly?
Pain or discomfort - *might indicate papilledema, raised IOP, variable leukemic infiltration*	• Do your eyes ever feel hurt, sore, or uncomfortable? • Have you ever had headaches that make it hard to see or make you feel sick?

Abbreviations: EOM, extraocular muscles; IOP, intraocular pressure; OGS, orbital granulocytic sarcoma.

of the global pooled prevalence of diabetic retinopathy in pediatric T2D within 2 years of diagnosis is 1.11%, despite screening not always being widely followed in practice.[46] The existence of such guidelines for T2D underscores the importance of implementing similar ophthalmic screening protocols for newly diagnosed leukemia patients. This is imperative to ensure early detection and prevention of long-term sequelae of ophthalmic disease which includes choroidal neovascularization and traction retinal detachments, both of which have the potential to result in rapid and severe vision loss if left untreated.[47]

Findings from the present study can be leveraged to make recommendations for screening. One approach involves the implementation of standardized screening questions for use by those who do not regularly assess and treat ophthalmic disease. Screening questions should be posed to children and their guardians at the time of leukemic work-up to assess vision changes, eye appearance, pain, and discomfort. Sample screening questions are provided in Table 1. Given the high rate of asymptomatic ophthalmic involvement, it is possible screening might warrant ophthalmic examination by a trained ophthalmologist. In that case, all newly diagnosed patients should be referred for screening by pediatric ophthalmology. A prospective study to better assess whether verbal screening is sufficiently effective in capturing ophthalmic involvement or if all newly diagnosed cases warrant referral to ophthalmology for complete examination is needed. Knowledge of the optimal timing and frequency of routine ophthalmic examinations throughout the disease course is also lacking.

The studies included in this review are diverse with respect to their aim and design, contributing substantial statistical heterogeneity to pooled prevalence estimates. As elaborated on previously, some included studies carried out full ophthalmic examinations in newly diagnosed patients in order to quantify the frequency of all observed ocular manifestations, whereas others pre-specified which ocular manifestation would be investigated prior to the study start. In cases where ocular manifestations were pre-specified, signs and symptoms that were not examined as part of the study question were not reported. This limitation might lead to an underestimation of the true prevalence of ocular involvement in this group.

Given the limitations of small sample sizes and high variability among studies, the estimates presented in this study should be interpreted with caution. For instance, CIs for prevalence estimates provided herein are wide which limits its precision. Further, in the case of symptomatic ocular involvement, meta-analyses yielded a non-significant estimate at the 95% confidence level. This emphasizes the need for more primary research in this area with larger patient cohorts, in order to minimize inter-study heterogeneity and the inherent statistical limitations that exist with estimates based on modest sample sizes.

Ocular involvement in pediatric leukemia is considered rare despite complete ophthalmic examination seldom being carried out at the time of diagnosis.[48,49] Given most patients in early disease stages are more likely to present with asymptomatic ophthalmic disease, the true prevalence of ocular involvement is unknown and likely underreported. The present study quantified the prevalence of ocular involvement across and within symptomatic and asymptomatic subgroups in order to better understand the true frequency of ophthalmic manifestations of this disease. Upwards of 1/5 of those with *de novo* leukemia will present with concurrent ophthalmic involvement, and estimates increase when separately assessing studies reporting asymptomatic findings. Findings from this review highlight

the importance of carrying out further research to assess the optimal approach to screening in this group.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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