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INVITED REVIEW

Occurrence and Case Fatality Rate of Invasive Aspergillosis in Children With Acute Leukemia: A Systematic Review and Meta-analysis

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Invasive aspergillosis (IA) is a potentially life-threatening complication of childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). We conducted a systematic review and meta-analyses of studies on acute leukemia in children aged 0–17 years since 2000. Findings were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We included 24 studies with 3661 ALL patients and 1728 AML patients. IA cumulative incidence varied (0%–10% for ALL and 0%–18% for AML) across the studies. Pooled cumulative IA incidences were estimated at 3.2% (95% CI: 1.8%–5.8%) in ALL and 5.2% (95% CI: 3.1%–8.6%) in AML, with corresponding case fatality rates of 13.3% (95% CI: 6.3%–25.9%), and 7.8% (95% CI: 0.7%–51.2%), respectively. Our analysis highlights the impact of IA in childhood leukemia, underscoring the need to address strategies for prevention, early detection, and treatment of IA in pediatric leukemia.

Key words. acute lymphoblastic leukemia; acute myelogenous leukemia; invasive aspergillosis; pediatric; systematic review.

INTRODUCTION

Invasive aspergillosis (IA) is the predominant mold infection in immunocompromised patients and causes significant morbidity and mortality in children and adolescents with acute leukemia (AL), particularly those receiving treatment for acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) or undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [1–3].

During recent decades, the options for treatment and prophylaxis have improved with an expansion in antifungal development, adding the newest class of antifungals, echinocandins, to the existing classes, including azoles, polyenes, and flucytosine [4, 5].

Also, diagnostic criteria, as those established in 2002 by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) and revised in 2008 and 2020, have altered the landscape of IA diagnosis [6–8]. Accordingly, the epidemiology of IA in childhood leukemia may have changed over recent decades.

Assessing the summarized incidence and case fatality rates (CFR) of IA represents a considerable challenge. No publication has compiled this information on the pediatric population from the post-millennial period. Consequently, decision-making regarding children may depend on single epidemiological studies or extrapolation from adult trials due to a lack of pediatric data [9]. To support clinical decision-making and to facilitate researchers designing future randomized trials for the prevention and management of IA, we conducted a comprehensive systematic review and meta-analysis presenting an overview of IA occurrence and CFR among children undergoing first-line or relapse treatment for AML or ALL. The current review highlights the continuing need to address strategies in the prevention, early detection, and treatment of IA in pediatric leukemia.

METHODS

We conducted a systematic review and meta-analysis reporting all findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. Before commencing the study, we registered the study protocol with the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42022349194) on August 9, 2022 [11].

Systematic Literature Search

A librarian-directed electronic database search, including Medline, Embase, and the Cochrane Central Register of

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Controlled Trials, was conducted on August 31, 2022, and updated on July 31, 2023. The search terms included "childhood," "acute," "leukemia," "aspergillus," and variations of these (see Supplementary 1 for the complete search strategy). The clinical trial registers ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched to identify unpublished studies [12]. The search period was limited to January 1, 2000, to July 31, 2023, with no further restrictions applied.

Study Selection

Study eligibility was based on the Condition, Context, Population (CoCoPop) framework for reviews assessing incidence data, with the condition being IA, the context being studies conducted from 2000, and the population consisting of non-HSCT children and adolescents (<18 years of age) undergoing first-line or relapse treatment for AL [13]. Eligible studies included interventional trials and observational studies with epidemiological data available for calculating incidence, risk factors, and/or CFR, and the provision of diagnostic criteria for IA, including, but not limited to, the EORTC/MSG criteria. To reduce reporting bias, case series were added to the list of excluded study types. Two reviewers (R. M. D. and M.R.) independently screened titles, abstracts, and full texts using reference management software (Covidence; Veritas Health Innovation Ltd) [14], resolving discrepancies through consensus, with the possibility of consulting a third author (J. B. M.).

Data Extraction

Data were extracted by one reviewer and checked for accuracy by a second independent reviewer.

Disagreements were resolved by consensus. When available, patient-level data were extracted for information on treatment, prophylaxis, risk factors, and outcomes. IA diagnoses were categorized as proven, probable, or possible according to EORTC/MSG guidelines. The possible category was excluded for research purposes as per EORTC/MSG recommendations [6–8]. Cases not designated as proven or probable were included only after verifying that the study excluded "possible" cases, and used internationally accepted guidelines as those by EORTC/MSG. Disseminated aspergillosis was defined as infection at more than one noncontiguous site. Only fatalities directly attributed to aspergillosis were included in the CFR. For ambiguous cases, we sought author clarification and excluded papers without a response.

Risk of Bias Assessment

No gold standard is available to assess the methodological quality of descriptive observational studies. Accordingly, we assessed the risk of bias (RoB) using a modified Joanna Briggs Institute (mJBI) checklist for prevalence studies [15]. The 9 questions were clarified to align with the objectives related to incidence and CFR. Six of these covered internal validity (ie, bias), and 3 covered other aspects (sample size calculation, reporting of study details, and statistical analysis). In the final assessment, we included the 6 internal validity questions.

This mJBI assessment either led to an overall low- or high risk of bias assessment (see Supplementary 2, Tables 5 and 6 for details on the mJBI checklist). For interventional studies, we treated each arm as a distinct observational study. Two reviewers independently assessed the risk of bias in the eligible studies (R. M. D. and M. R.).

Analysis and Assessment of the Evidence

"Cumulative incidence" was defined as the rate of IA cases per patient observation course (the IA risk periods, ie, the complete leukemia disease course or intensive treatment courses). Since the included studies were of different types and not consistently designed to report incidence or prevalence rates, all studies were standardized by extracting data on the population size, the number of IA cases, and the number of IA-related deaths. Each patient was counted only once. CFR represented the proportion of IA cases that led to IA-related deaths.

We used a generalized linear mixed-effects model via the *metaprop* function in R (R Core Team, 2022), which includes an inherent data transformation, to analyze cumulative IA incidence and CFR across the full data set, and the low and high RoB subgroups individually [16, 17]. Logit transformation addressed nonnormal distributions. Results were back-transformed and reported according to the random effect model. p values < .05 were considered statistically significant. Study heterogeneity was assessed with Forest plots and I^2 statistics: 0%–40% (insignificant), 30%–60% (moderate), 50%–90% (substantial), and 75%–100% (considerable) [18]. If I^2 was zero due to too few analyzed studies, it was not reported. To compare 2 groups, we employed the 2-sample z-test to assess significant differences. Funnel plots and Egger's test were employed to examine reporting bias.

RESULTS

As of August 31, 2022, our database searches yielded 4379 studies, with an additional 310 found at the July 31, 2023, update. Of these, 24 eligible studies were included for data extraction. Figure 1 summarizes the results of the study screening process.

Study Description

Study characteristics are summarized in Table 1 (full data set available in Supplementary 2, Tables 1–4). Of the total 24 included studies, 6 reported exclusively on AML [1, 22, 23, 31, 34, 40], 5 exclusively on ALL [3, 19, 26, 38, 39], and 13 reported on both [20, 21, 24, 25, 27–30, 32, 33, 35–37]. There were 5 prospective and 18 retrospective studies, 1 nonrandomized

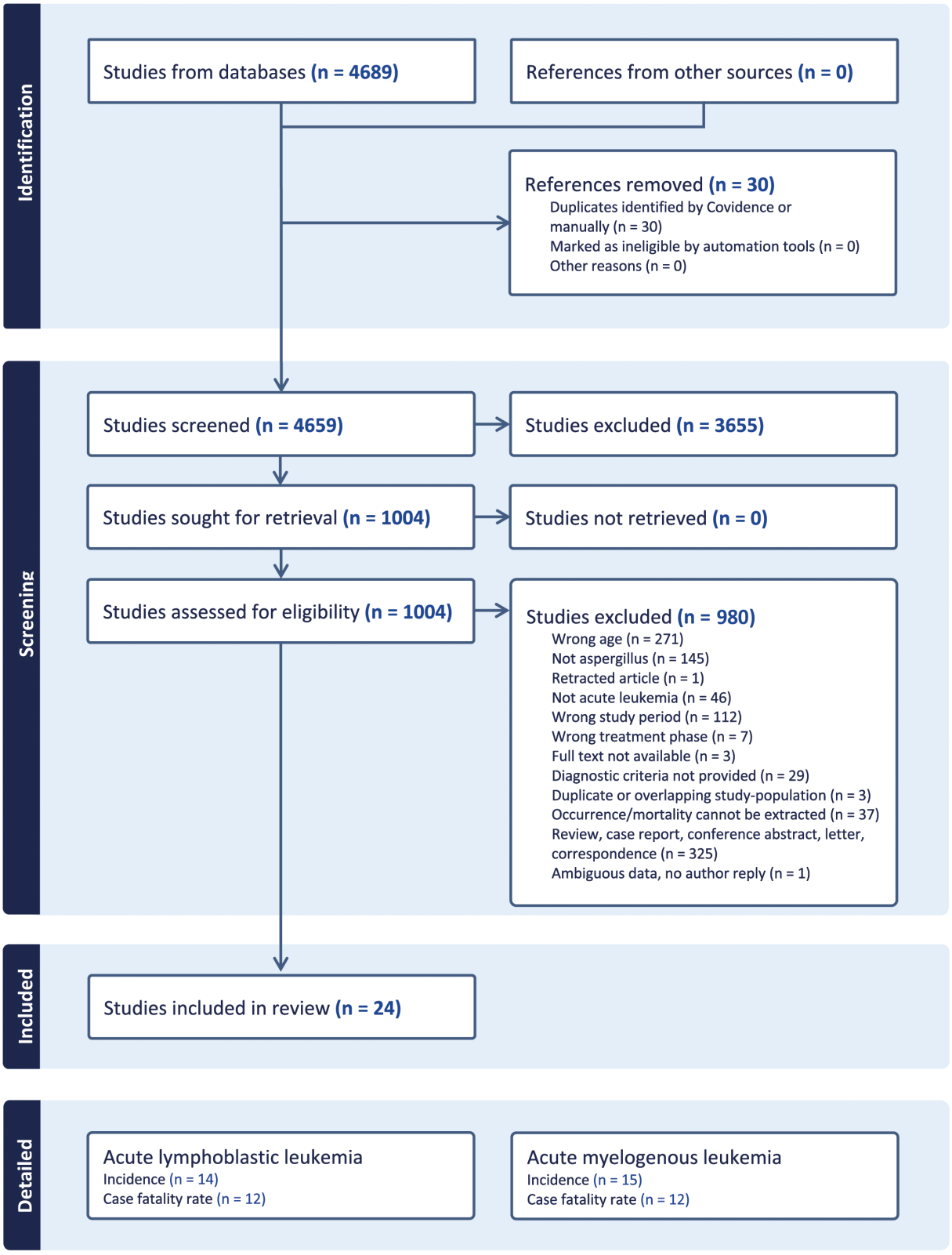

Figure 1. Flow diagram of the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Table 1. Summarized Characteristics and Quality Assessment of the 24 Studies Included in the Systematic Review on Invasive Aspergillosis in Acute Childhood Leukemia

Study	Study Design	Country	EORTC Criteria	Sample Size ALL	IA Cases ALL	Fatalities ALL	Sample Size AML	IA Cases AML	Fatalities AML	Surveillance Period	mJBI Quality Assessment ALL		mJBI Quality Assessment AML	
											Incidence	CFR	Incidence	CFR
Bal et al [19] (2015)	RS	Turkey	2008	125	12	0				WT	Low risk	Low risk		
Barbor et al [20] (2012)	RS	Germany	2008	128	1	n/a	58	10	n/a	WT	Low risk	n/a	Low risk	n/a
Baytan et al [21] (2009)	RS	Turkey	2008	129	12	3	22	2	0	WT	Low risk	Low risk	Low risk	Low risk
Bochennek et al [22] (2016) and Hassler et al [23] (2016)[a]	PS	Germany	2008				466	10	3	Non-DS: IT. CFR followed for at least 160 days. DS: WT.			Low risk	Low risk
Cakir et al [24] (2010)	RS	Turkey	2002	n/a	2	1	n/a	1	1	WT	n/a	Low risk	n/a	Low risk
Döring et al [25] (2015)	RS	Germany	2002 + 2008	41	1	0	21	1	0	WT	High risk	Low risk	High risk	Low risk
Fischer et al [26] (2018)	RS	Germany	2008	2307	30	n/a				WT	Low risk	n/a		
Hovi et al [27] (2007)	PS	Finland	2002	58	0	n/a	2	0	n/a	AML: WT. ALL: One year after induction phase.	Low risk	n/a	Low risk	n/a
Jha et al [28] (2013)	PS	India	2002	n/a	1	1	n/a	1	0	WT	n/a	Low risk	n/a	Low risk
Kazakou et al [29] (2020)	RS	Greece	2008	181	10	2	22	4	3	WT	Low risk	Low risk	Low risk	Low risk
Lehrnbecher et al [30] (2019)	PS	Germany, Austria	2008	151	4	0	28	2	0	One year after IT.	Low risk	Low risk	Low risk	Low risk
Lin et al [31] (2018)	RS	Taiwan	2008				78	4	2	WT			Low risk	Low risk
Meena et al [32] (2019)	RS	India	2008	n/a	5	1	n/a	4	1	WT	n/a	High risk	n/a	High risk
Pana et al [33] (2018)	RS	Greece	2008	127	0	n/a	19	0	n/a	Two weeks before prophylaxis to 4 weeks after.	High risk	n/a	High risk	n/a
Rivaud et al [34] (2013)	RS	France	2008				387	12	0	WT			Low risk	Low risk
Simon et al [35] (2007)	PS	Germany	2002	6	0	n/a	9	0	n/a	WT	High risk	n/a	Low risk	n/a
Supatharawanich et al [36] (2021)	RS	Thailand	2008	150	6	n/a	35	1	n/a	WT	Low risk	n/a	Low risk	n/a
Vissing et al [37] (2021)	RS	Denmark	2002 + PCR	24	4	0	38	6[b]	0	IT	High risk	High risk	Low risk	Low risk
Wang et al [3] (2019)	RS	Australia	2008 + PCR	n/a	33	2				WT	n/a	Low risk		
Yeoh et al [1] (2021)	RS	Australia	2020				232	11	0	WT			Low risk	Low risk
Yeoh et al [38] (2022)	NRES	Australia	2020	133	2	0				Only CFR use: During bridging treatment, to the end of study period median 24 month.	High risk	High risk		
Yunus et al [39] (2014)	RS	Germany	2008	101	4	1				EM	Low risk	Low risk		
Zając-Spychała et al [40] (2019)	RS	Poland	2008				311	6	n/a	WT			Low risk	n/a

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CFR, case fatality rate; DS, Down syndrome; EM, excluding maintenance; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG); IT, intensive treatment phases; mJBI, modified Joanna Briggs Institute (mJBI) Critical Appraisal Tool for studies reporting prevalence data; n/a, not applicable; NRES, nonrandomized experimental study; PS, prospective cohort study; RS, retrospective cohort study; WT, whole treatment course.

[a]Studies are combined as they originate from the same cohort; one study focuses on participants without trisomy 21, while the other exclusively examines those with trisomy 21.

[b]Two cases of biphenotypic leukemia counted as AML.

experimental study, and no randomized studies meeting the eligibility criteria. All studies employed the EORTC/MSG diagnostic criteria.

Quality Assessment

For ALL, 14 studies were quality assessed for the incidence objective. Nine had low RoB, while the other 5 had high RoB. Of the 13 studies quality assessed for CFR, 9 had low RoB, while 4 had high RoB.

For AML, 15 studies underwent quality assessment for the incidence objective, with 13 showing low RoB and the other 2 showing high RoB. Of the 12 studies quality assessed for CFR, 11 showed low RoB, while 1 showed high RoB. In both types of leukemia, the primary factor contributing to a high RoB was a risk of selection bias (see Table 1, with details in Supplementary 2, Tables 5 and 6).

Invasive Aspergillosis Incidences

The IA cumulative incidence in ALL, as reported in 14 studies covering 3661 children and 86 IA cases, exhibited significant variability, ranging from 0% [27, 33, 35] to 17% [37] across both RoB groups. The overall pooled cumulative incidence was 2.8% (95% CI: 1.5%–5.1%) and 3.2% (95% CI: 1.8%–5.8%) in low RoB studies, showing substantial heterogeneity (I^2 = 81.7%). RoB subgroup analysis revealed no significant differences in IA rates (Figure 2A and C).

Among the cases, 11 (12.8%) were categorized as "proven," 43 (50.0%) as "probable," and 32 (37.2%) were unspecified. The infection site was pulmonary in 39 cases (45.4%), disseminated in 13 cases (15.1%), sinus in 4 cases (4.7%), and central nervous system in 4 cases (4.7%). In the remaining 26 cases (30.2%), the site of infection was not specified.

In AML, IA cumulative incidence ranged from 0% [27, 33, 35] to 18% [29] with a pooled cumulative incidence of 4.9% (95% CI: 3.0%–7.9%) across all studies and 5.2% (95% CI: 3.1%–8.6%) in the low RoB studies, comprising a total 1728 children and 69 IA cases. AML subgroup analysis by RoB showed no significant difference in IA occurrence (Figure 2B and D). Of the cases, 14 (20.3%) were categorized as "proven," 38 (55.1%) as "probable," and 17 (24.6%) were unspecified. The infection site was primarily pulmonary in 35 cases (50.7%), disseminated in 4 cases (5.8%), sinus in 2 cases (2.9%), and skin in 1 case (1.5%). In 27 cases (39.1%), the site of infection was not specified.

Results of Eggers tests and funnel plots are available in Table 2 and Figure 2, respectively.

Case Fatality Rate Related to Invasive Aspergillosis

In ALL, 12 studies reported 90 cases of IA with 11 IA-related fatalities resulting in a crude CFR of 12.2%. The CFR meta-analysis found a pooled CFR of 12.4% (95% CI: 6.5%–22.4%) regardless of RoB. The 9 low RoB studies showed a CFR of 13.3% (95% CI: 6.3%–25.9%), with minimal heterogeneity (Figure 3A and C).

In AML, 12 studies described 58 cases of IA with 10 fatalities resulting in a crude CFR of 17.2%. The CFR meta-analysis found an overall pooled CFR of 11.0% (95% CI: 1.9%–43.6%) and 7.8% (95% CI: 0.7%–51.2%) in the 11 low RoB studies, with no significant interstudy heterogeneity, I^2 (Figure 3B and D).

Results of Eggers test and funnel plots are available in Table 2 and Figure 3.

Invasive Aspergillosis Occurrence by Treatment Phase

Information regarding IA occurrences during specific treatment phases was limited, with only 5 studies reporting on 18 IA cases in primary ALL patients [21, 28–30, 38] and 5 studies reporting on 19 IA cases in primary AML patients [28–31, 34].

In ALL patients, IA was mainly observed during induction (n = 16) or reinduction (n = 2), with no reported cases during later treatment phases. For AML patients, IA was primarily documented during induction (n = 13), during consolidation 1 (n = 1), 2 (n = 1), 3 (n = 3), and the reinduction phase (n = 1). Whereas reinduction is not a typically defined AML treatment phase, this may stem from a different terminology used by the authors. Data are reported as presented [30].

Subgroup Analyses

Invasive aspergillosis cumulative incidence was lower in ALL than AML, but the difference was nonsignificant. Prophylaxis data were sparse: in ALL, data were available from 5 studies covering 183 leukemia patients who received mold-active prophylaxis and 140 who did not; among the 86 IA cases, 4 received prophylaxis, 13 did not, and 69 had no prophylaxis data. In AML, 6 studies reported on 86 leukemia patients who received mold-active prophylaxis and 466 who did not; out of 69 IA cases, 7 received prophylaxis, 21 did not, and 41 had no prophylaxis data. Data scarcity in the included studies limited our analysis of IA incidence and antifungal prophylaxis impact (results in Table 2). Additionally, examining the impact of leukemia risk stratification (including primary or relapsed disease) (results in Table 2), steroid exposure, and neutrophil count on IA risk or mortality was limited by data inconsistencies and sparsity (data can be found in Supplementary 2, Tables 1 and 2).

DISCUSSION

Invasive aspergillosis is a serious complication of childhood leukemia, with varying reported incidences and CFR. In this systematic review and meta-analysis, we provide an updated comprehensive estimate of the incidence of IA during treatment for childhood ALL and AML.

In ALL, IA cumulative incidence varied widely among studies, resulting in a pooled cumulative incidence of 3.2% (95% CI: 1.8%–5.8%) in low ROB studies. This result is supported by

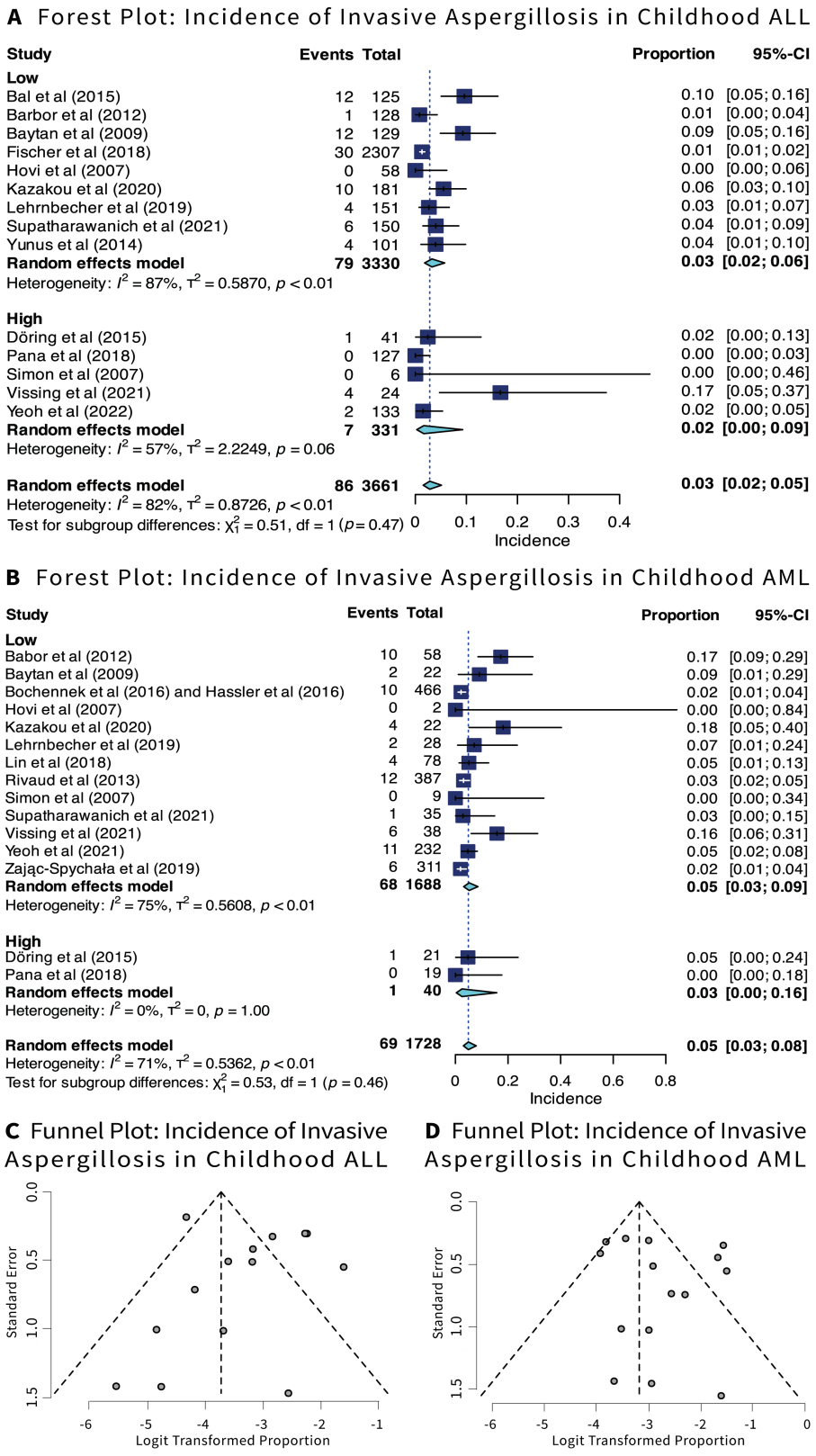

Figure 2. Forest plots (A, B) display the pooled cumulative incidence of invasive aspergillosis (IA) in childhood acute lymphoblastic leukemia (ALL) (A) and acute myeloid leukemia (AML) (B), divided by the risk of bias (Low, High). Panels C and D contain funnel plots for the corresponding forest plots.

Table 2. Summary of Meta-Analytic Findings of Invasive Aspergillosis Incidence and Case Fatality Rates in Childhood Leukemia. The Analysis Covers Pooled Incidences, Case Fatality Rates, and Subgroup Comparisons, Including Low and High-Risk Bias, Primary and Relapse Leukemia, and Prophylaxis Impact

Factor	Subgroup	Studies (*n*)	Observations (*n*)	Events (*n*)	Proportion (%)	95% CI (%)	I^2 (%)	*p* Value	Significant Risk (Y/N)
ALL									
Pooled IA incidence	Total	14	3661	86	2.8	[1.5, 5.1]	81.7		Y
	Low risk of bias	9	3330	79	3.2	[1.8, 5.8]	86.5		
	High risk of bias	5	331	7	1.6	[0.3, 9.3]	56.7		
	Subgroup diff.							NS	
IA incidence vs primary/relapsed ALL	Primary ALL	8	700	17	2.1	[0.9, 4.9]	2.7		Y
	Relapsed ALL	4	45	2	2.3	[0.1, 46.7]	0.0		N
	Comparison							NS	
IA incidence vs ± prophylaxis	No prophylaxis	2	140	13	9.3	[5.5, 15.3]	0.0		n/a
	Prophylaxis	4	183	4	0.2	[0.0, 56.0]	0.0		N
	Comparison							NS	
IA-related CFR	Total	12	90	11	12.4	[6.5, 22.4]	0.0		Y
	Low risk of bias	9	79	10	13.3	[6.3, 25.9]	0.0		
	High risk of bias	3	11	1	9.1	[1.3, 43.9]	0.0		
	Subgroup diff.							NS	
AML									
Pooled IA incidence	Total	15	1728	69	4.9	[3.0, 7.9]	70.8		Y
	Low risk of bias	13	1688	68	5.2	[3.1, 8.6]	75.0		
	High risk of bias	2	40	1	2.5	[0.4, 15.7]	0.0		
	Subgroup diff.							NS	
IA incidence vs primary/relapsed AML	Primary AML	8	772	27	4.0	[1.6, 9.6]	76.1		Y
	Relapsed AML	4	95	2	1.3	[0.1, 23.1]	0.0		N
	Comparison							NS	
IA incidence vs ± prophylaxis	No prophylaxis	3	466	16	3.4	[2.1, 5.5]	0.0		Y
	Prophylaxis	5	86	7	5.1	[0.9, 24.6]	0.0		N
	Comparison							NS	
IA-related CFR	Total	12	58	10	11.0	[1.9, 43.6]	0.0		N
	Low risk of bias	11	54	9	7.8	[0.7, 51.2]	0.0		
	High risk of bias	1	4	1	25.0	[3.4, 76.2]	n/a		
	Subgroup diff.							NS	

I^2 statistics show the study heterogeneity within each meta-analysis. Significant risk of publication bias, as assessed by Egger's test and indicated by "yes" if $p < .05$ or "no" if $p > .05$.
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CFR, case fatality rate; Diff., difference; I^2 statistics; IA, invasive aspergillosis; *n*, number; *N*, no; n/a, not applicable; NS, not significant; Pub. bias, risk of publication bias; vs, versus; Y, yes.

a sample size of 3330 ALL patients and 79 IA cases. In comparison, a lower cumulative incidence of 1.6% was reported in a French national study, encompassing patients up to 19 years [41]. Notably, over half of these patients received antifungal prophylaxis. While this study reported on 1531 ALL patients, it represented a smaller sample compared to this systematic review, and a more homogeneous cohort.

In AML, the IA cumulative incidences also varied widely across the studies resulting in a pooled cumulative incidence of 5.2% (95% CI: 3.1%–8.6%) in low ROB studies. The reliability of this result is supported by a sample size of 1688 AML patients and 68 IA cases. A cumulative incidence that was higher than in ALL was expected. Notably, a recent multicenter study reported a similar cumulative incidence of 5.8% in primary AML in patients aged up to 19 years, where over half received prophylaxis [41]. It is important to consider that our analysis includes a mixed study population of both primary and relapsed leukemia and varying use of prophylaxis. The Vissing et al. study, describing a 7-patient *Aspergillus flavus* outbreak over 2017–2019, prompted bias concerns [37]. Given the prolonged period and the limited number of cases, we decided to retain the study. The infection source remained unidentified, though hospital renovations were suspected, aligning with known construction-related mold risks [42]. The IA cumulative incidence was 16% in AML, not the highest in our review, and 17% in ALL, categorized in ALL's high RoB group.

In our study, IA pooled cumulative incidences in primary and relapsed ALL were similar: 2.1% and 2.3%, respectively (see Table 2). We would expect a higher cumulative IA incidence in relapsed ALL, as also seen in a comparable study of 1360 de novo and 171 relapsed ALL patients, in which the rates were

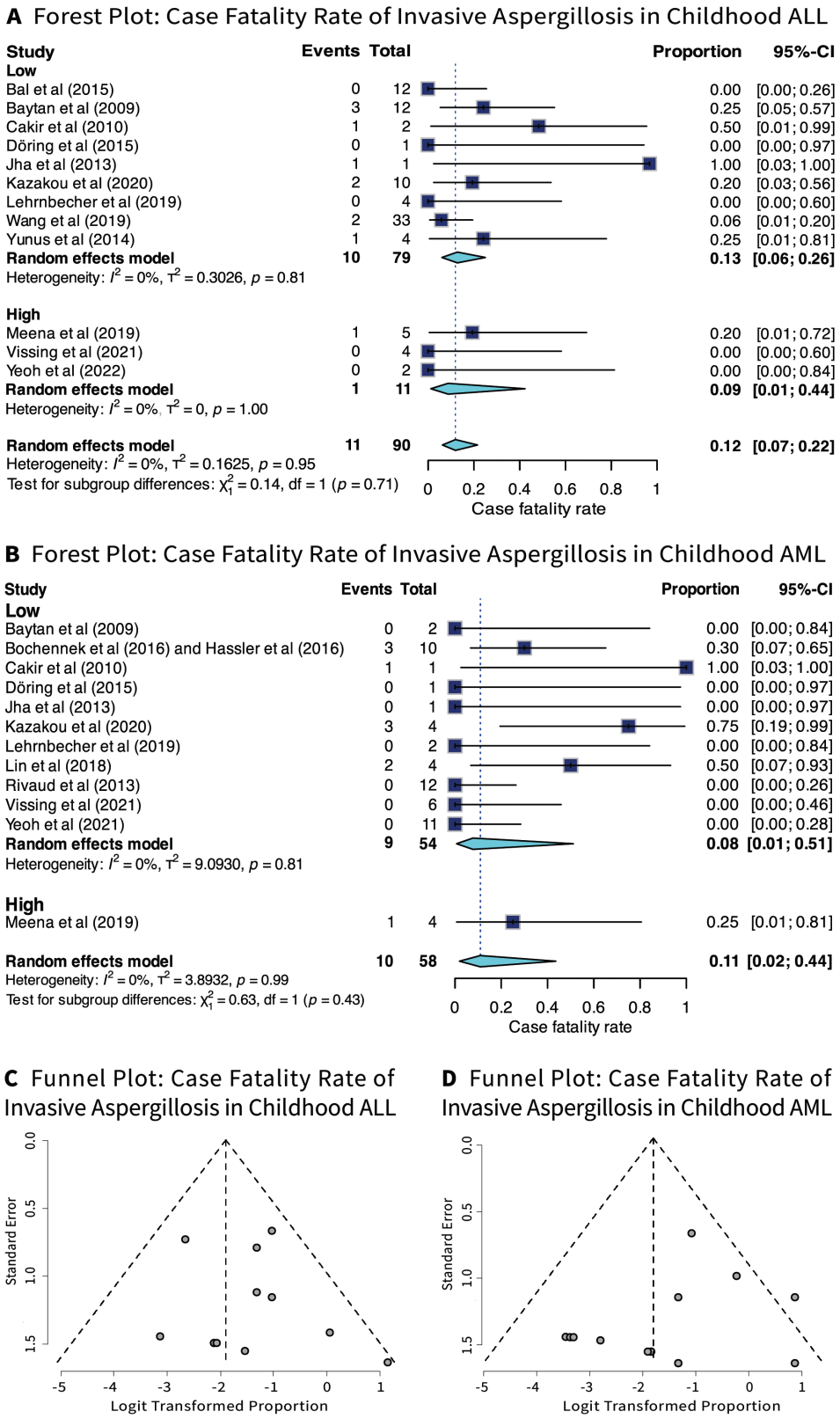

Figure 3. Forest plots (A, B) display the case fatality rate of invasive aspergillosis (IA) in childhood acute lymphoblastic leukemia (ALL) (A) and acute myeloid leukemia (AML) (B), divided by the risk of bias (Low, High). Panels C and D contain funnel plots for the corresponding forest plots.

1.3% and 3.5%, respectively [41]. In the current study, the figure for relapsed cases was more uncertain and supported by fewer cases, highlighting the need for additional data for this patient group.

Similarly, for AML, the pooled cumulative incidences were 4.0% in primary leukemia and only 1.3% in relapsed leukemia, with nonsignificant subgroup differences. However, the small sample size of AML relapse (n = 95) and the occurrence of only 2 IA cases challenge drawing robust conclusions in this subgroup. Additionally, comparing primary to relapsed leukemia encounters methodological issues due to different risk periods, immune status, and prophylaxis strategies, complicating direct comparisons and interpretation.

While international guidelines recommend antifungal prophylaxis for AML, evidence for its efficacy in nontransplanted childhood ALL is still emerging, with current recommendations often informed by adult trials and pediatric pharmacology studies [41, 43]. We observed IA pooled cumulative incidence rates of 9.3% (95% CI: 6.0%–15.0%) in ALL patients without prophylaxis, in contrast to 0.2% (95% CI: 0.0%–56.0%) in the prophylaxis group, suggesting a benefit of prophylaxis. Nonetheless, on comparison, no significant difference was found. However, our primary objectives were to determine overall pooled cumulative incidences and CFR and not to compare prophylaxis strategies. Furthermore, these results are limited due to the small number of studies, particularly in the prophylaxis group.

In the AML subgroup, the pooled cumulative incidence without prophylaxis was 3.4% (95% CI: 2.1%–5.5%), which aligns with a study conducted before 2000, reporting a 3.3% pooled cumulative incidence among 304 childhood AML cases [44]. However, among the 86 patients with prophylaxis, we observed a 5.1% pooled cumulative incidence (95% CI: 0.87%–24.64%), which might be misleading due to the previously mentioned scenario, with breakthrough infections from a single paper on an *A flavus* outbreak, in patients receiving liposomal amphotericin-B prophylaxis [37]. Subgroup differences were nonsignificant. However, previous evidence does support antifungal prophylaxis in childhood AML [45–47].

Invasive fungal infections are a significant cause of mortality in AL. Our CFR, at 13.3% for ALL and 7.8% for AML, is notably lower than reported in a study retrospectively analyzing IA outcomes in 36 patients with ALL and 31 patients with AML [48]. However, this study also included cases from HSCT patients, and figures are thus not directly comparable. Furthermore, the figures given above are a result of the meta-analysis in low ROB studies and notably lower than the crude CFR of 17.2% underlining the need for further knowledge in this area.

Methodological Considerations

This systematic review and meta-analysis provide an aggregate estimate of IA pooled cumulative incidence and mortality among pediatric leukemia patients. The estimates are based on 24 studies that adhered to strict inclusion criteria and quality assessments and employed consistent diagnostic criteria, minimizing diagnostic bias. However, these meta-analyses have limitations, as most included studies were retrospective, several were not designed for epidemiological purposes, had limited sample sizes, and showed limited geographical distribution, lacking studies from America and Africa, introducing the risk of bias. Additionally, we included only studies with participants under 18, excluding those with mixed adult and pediatric age groups. Consequently, considerable pediatric data were not used in this meta-analysis. However, this choice was made in order to present representative pediatric data. Various degrees of publication bias were suggested by funnel plots analysis and Egger's tests. While we sought to mitigate bias by searching for unpublished studies, our focus on robust studies may introduce bias. The observed asymmetry suggests studies with the potential to bias the meta-analysis but does not explain the cause underlining the continued need for data in this field [49].

Moreover, while all studies surveilled IA during intensive treatment phases, not all reported from the entire treatment period [22, 27, 30, 33, 37–39]. To compensate for this, 2 studies with the shortest surveillance periods were assessed as high RoB. The remaining studies had longer surveillance periods, which reduces the risk of missing IA cases, as these primarily occur during the intensive treatment phases [50]. Lastly, although a total of 5389 patients with AL and 202 IA cases were included in the incidence, CFR, or both meta-analyses, the sample size within each analysis of potential risk factors was limited. The main objective of the meta-analysis was to provide an overview of IA occurrence and CFR among children undergoing first-line or relapse treatment for AML or ALL. This included pooling data from sometimes heterogeneous subpopulations (eg, some received prophylaxis, and some did not), which should be considered when interpreting the results. Nevertheless, the results from all subgroups are presented in Table 2, allowing for a detailed understanding of the heterogeneous subgroups.

In conclusion, despite the availability of modern antifungal therapies and diagnostics, this systematic review and meta-analysis covering the literature from the last 2 decades highlights the impact of IA in childhood leukemia, underscoring the continuing need to address strategies for prevention, early detection, and treatment. Future studies should employ consistent diagnostic criteria and case definitions. Prospective and uniform registering of fungal infections will reduce the risk of detection bias and help identify all cases of IA to support clinical decision-making, improve prophylactic strategies, and facilitate designing future trials.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Notes

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Data Availability

Data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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