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Fungi and Fungal Diseases

Risk factors for invasive mould infections in adult patients with hematological malignancies and/or stem cell transplant: A systematic literature review and meta-analysis



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SUMMARY

Objectives: To evaluate risk factors for invasive mould infections (IMI) in adult patients with hematological malignancies and/or hematopoietic stem cell transplantation (HSCT).

Methods: Systematic review from PubMed, Embase, CENTRAL, and grey literature (01/01/2002–23/01/2025). Eligible studies were cohort or case-control studies. Selection, data extraction, and bias assessment were performed in duplicate. Adjusted measure effects were pooled using random-effects models.

Results: From 13,372 references, 45 studies were included; 17 focused on any type of IMI (n=846), 26 specifically on invasive aspergillosis (IA, n=2086) and 2 on mucormycosis (n=53). Twenty-eight studies (10 on IMI, 18 on IA) were eligible for meta-analysis. Relapsed/refractory hemopathies were significantly associated with a higher risk of IMI (HR 3.43 [95%CI 1.58–7.46]) whereas prolonged neutropenia was associated with IA (OR 4.85 [95%CI 2.15–10.97]). Specifically in the allo-HSCT population, both acute and chronic graft vs host disease (GvHD) (acute GvHD HR 3.23 [95%CI 2.20–4.74]; chronic GvHD HR 2.95 [95%CI 1.25–6.96]) were associated with IMI and CMV disease (HR 3.23 [95%CI 1.00–10.43]), and corticosteroid use (HR 4.67 [95% CI 2.79–7.82]) were associated with IA.

Conclusion: Recognizing risk factors for IMI in patients with hematological malignancy or HSCT is essential to improve prevention and management strategies.

Registration: PROSPERO, CRD42023429103.

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Introduction

Invasive mould infections (IMI) remain a major complication in patients with hematological malignancies, especially in patients who undergo hematopoietic stem cell transplantation (HSCT). Among these infections, invasive aspergillosis (IA) is the most prevalent, with an estimated global annual incidence of 27,000 cases among 173,629 patients with acute myeloid leukemia (AML) and allogeneic HSCT (allo-HSCT).¹ While IA dominates IMI in this population, mucormycosis also poses a serious threat, albeit at a lower

frequency.² Between 2001 and 2006, its 12-month cumulative incidence was estimated in the United States at 0.28% in HSCT recipients, and up to 0.80% in allo-HSCT recipients from unrelated donors.² In France, this incidence has also risen over time, from 0.02 cases/million persons in 1997 to 0.2 cases/million persons in 2006 in patients with hematological malignancy.³

Despite advances in antifungal therapy, IMI remains associated with high mortality. When treated, IA carries a global mortality rate of 45% (ranging from 30% to 57%), accounting for an estimated annual 11,000 attributable deaths worldwide.¹ Mucormycosis is associated with an even higher mortality rate, estimated at 60.3% [95% confidence interval (CI) 42.7–77.9] for pulmonary infections worldwide.⁴ In France, a 3-month mortality of 64% was reported among patients with hematological malignancies for all forms of mucormycosis.⁵

Identifying risk factors for IMI is essential to optimize antifungal prophylaxis and facilitate earlier diagnosis. Ongoing research in this area remains important as treatments for hematological malignancies and HSCT continue to evolve and may introduce new vulnerabilities. Risk factors are commonly categorized into patient characteristics, hematological disease or transplant-related factors, biological parameters, treatments and environmental fungal exposure.⁶ The adoption of standardized definitions first introduced in 2002 and updated in 2008 and 2020 by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) has facilitated research on IMI.^{7–9} Three diagnostic categories are defined: proven (requiring mycological evidence from a sterile site), probable (based on host factors, clinical features, and mycological evidence), and possible (based on host factors and clinical features without mycological evidence). The most recent update in 2020 placed particular emphasis on the limited reliability of possible cases in research settings. A recent meta-analysis examined risk factors for IMI specifically in HSCT patients but it did not focus on adult populations or studies published after the establishment of consensus definitions.¹⁰

We conducted a systematic review to assess risk factors for IMI specifically in adult patients with hematological malignancies and/or HSCT, alongside two separate meta-analyses based on EORTC/MSG definitions: one limited to studies including proven and/or probable IMI to identify high certainty risk factors, and one including possible IMI cases to account for undiagnosed IMI cases prior to modern diagnostic advancements.

Methods

Study design

This systematic review and meta-analysis were conducted according to the Cochrane Handbook and follow the PRISMA-2020 (additional file 1) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statements.^{11,12} The study protocol was registered with PROSPERO on June 3rd, 2023 (CRD42023429103), with any modifications detailed in additional file 2.

Eligibility criteria

Studies were included if they met the following criteria: 1) cohort or case-control study, 2) $\geq 90\%$ of patients aged 18 or older, 3) $\geq 90\%$ of patients with a hematological malignancy and/or having received a HSCT, 4) published after January 1st, 2002, 5) reporting the number of patients with IMI and risk factors. The January 1st, 2002 cutoff aligns with the first EORTC/MSG consensus definitions for invasive fungal infections (IFI).⁷ In cases where additional information from the authors could not be obtained, studies containing patients aged 16 and older were included and classified as including adults and children.

Exclusion criteria were: 1) no assessment of IFI-associated factors; 2) fewer than 10 patients in any group; 3) insufficient reporting of patient characteristics; 4) genetic risk factors; 5) IFI types other than IMI.

There was no restriction on publication language, and authors were contacted if the publication was unavailable.

Search strategy

Relevant articles were identified through:

- 1) an electronic search in Medline through PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). The search algorithms included Medical Subject Headings (MeSH) or Embase Medical headings (EMTREE) and free text words for observational studies, invasive fungal infections, hematological malignancies or HSCT in adult patients (additional files 3–5).
- 2) a grey literature search through ClinicalTrials.gov database, the International Clinical Trials Registry Platform and through the screening of abstracts of the congresses of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID, 2002–2024) and of the Infectious Disease Society of America (IDSA, 2003–2024).
- 3) a screening of the reference list of the identified publications and of available reviews.

Initial search was performed on February 2023 and updated on January 23rd, 2025.

Study selection

After duplicate removal, one reviewer (EG) screened articles based on title and abstract. Then, two reviewers independently assessed full texts for eligibility (EG reviewed all articles, while LA and PMG divided the remaining workload). Discrepancies were resolved through consensus or adjudication by the third reviewer. Study selection was conducted using Rayyan.¹³

Data extraction

Two reviewers independently extracted data using a standardized form (EG extracted all studies, while LA and PMG shared the work equally). They evaluated the type of IMI reported in each study (i.e., IMI any type, IA or invasive mucormycosis), the IFI definition used (EORTC/MSG or other) and the level of diagnostic certainty—either proven and/or probable IFI, or including possible cases as well. Additional extracted data included general study characteristics, baseline population details, and hematological history. Univariate and multivariate analysis results were also recorded, including effect measures, adjusted effect measures, 95%CI, and adjustment factors. Studies could use either patients or episodes as the denominator. An episode referred to a hospital admission or care period (e.g., remission induction chemotherapy), meaning a patient could be included in both IFI and no-IFI groups based on episode characteristics. For HSCT recipients, the extraction included the specific period during which risk factors were assessed—early (1–39 days), late (40–100 days), or very late (101–365 days) post-transplant—if specified.

At any stage, if information was missing, authors were contacted by email for clarification.

Methodological quality assessment

Two reviewers independently evaluated the methodological quality of the included studies using the Critical Appraisal Skills Programme (CASP) checklists for cohort studies and case-control

studies.^{14,15} These tools evaluate key aspects of the study design – such as population recruitment, measurement of exposures and outcomes, and consideration of confounding factors – as well as the precision of the results. Based on the answers, studies were classified as methodologically sound or relatively poor. EG reviewed all articles, while LA and PMG equally shared the assessments.

Analyses

For the qualitative synthesis, all studies meeting the inclusion criteria were analyzed. Wherever applicable, OR and 95%CI were calculated.¹⁶ All variables significantly associated with IFI in univariate analysis were reported, along with results for all variables included in multivariate models, regardless of statistical significance.

The primary meta-analysis included studies assessing proven and/or probable IFI based on EORTC/MSG classifications and reporting adjusted effect measures. A secondary meta-analysis incorporated studies also considering possible IFI based on the 2002 and 2008 EORTC/MSG definitions. HR, sub-distribution HR (SHR), and RR were pooled together, while OR and HR (or equivalents) were analyzed separately. For each potential risk factor, the specific population studied (e.g., AML) was noted when relevant and subgroup analyses by focusing on particular patient populations (e.g. AML/MDS patients or allo-HSCT recipients) were performed whenever possible. Given the expected high between-study heterogeneity, random-effects models were used. Heterogeneity was assessed through visual inspection of forest plots, the Q Cochran heterogeneity test, and I².

Preplanned sensitivity analyses included excluding studies with a relatively poor methodology (for both proven and/or probable IMI and proven, probable and/or possible IMI), studies including children, and studies using episodes as the denominator for proven and/or probable IMI.

All analyses were conducted using R software (version 4.4.0) with the meta package and *metagen* function.¹⁷

To improve clarity, the results section will focus on data related to proven and/or probable infections, specifying the type of IMI assessed (e.g., IMI any type or IA). Information including possible infections is reported only when relevant, with this explicitly stated in the text, and available in additional files.

Grading of evidence

The GRADE approach was used to assess the grading of evidence for each potential risk factor.¹⁸

Results

Selection process and characteristics of included studies

From a total of 13,372 identified references, 547 studies underwent full-text assessment, with 45 ultimately included in the systematic review (17 studies reported any type of IMI, 26 studies reported exclusively on IA, and two on mucormycosis) (Fig. 1, Table 1 and additional file 6). Reasons for exclusion based on full-text assessment are listed in additional file 7. Three studies reported results on episodes rather than patients. These episodes were based on hospital admissions for two and on remission-induction chemotherapy for one. Across all included studies, a total of 846 IMI was reported among 13,822 episodes assessing any type of IMI, 2086 cases of IA were identified among 135,776 episodes specifically evaluating IA, and 53 cases of mucormycosis were reported among 77 episodes in studies focusing on this infection. Among studies reporting on any type of IMI, the main species remained *Aspergillus*. Details on IMI types are given in additional file 6 when available. Among the 45 studies included in the systematic review, 35 (78%) were considered methodologically sound and 10 (22%) relatively poor (additional files 8 and 9).

A total of 28 studies (10 on any type of IMI and 18 focusing on IA, as per EORTC/MSG definitions) provided adjusted measure effects for risk factors evaluated in multiple studies, thereby qualifying for

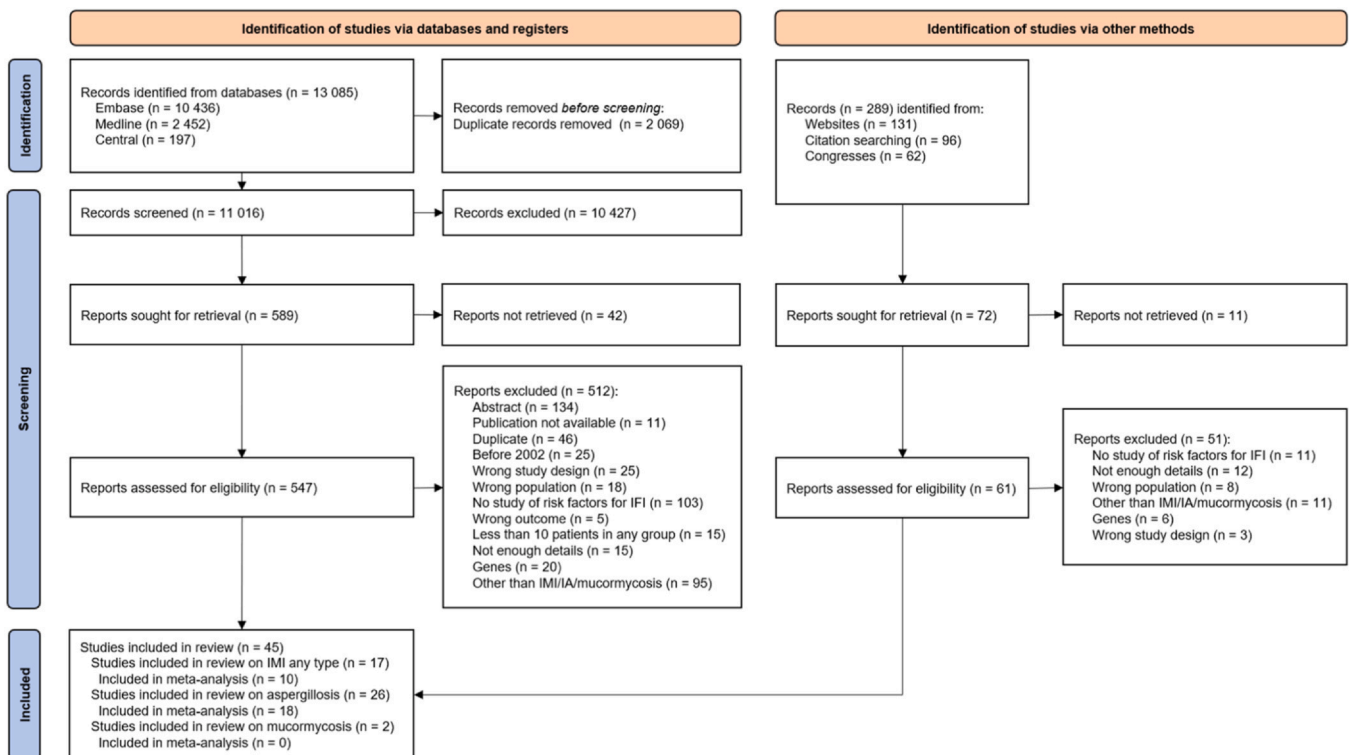


Fig. 1. Flow chart. IMI, invasive mould infection; IA, invasive aspergillosis.

Table 1
Studies included in the systematic review (n = 45) and in the meta-analysis (n = 28).

	IMI		Aspergillosis		Mucormycosis
	Systematic review (N = 17, %)	Meta-analysis (N = 10, %)	Systematic review (N = 26, %)	Meta-analysis (N = 18, %)	Systematic review (N = 2, %)
Study period					
Beginning study period (median, IQR)	2008.5 (2005–2010)	2005 (2004–2009)	2005 (2000–2007)	2005 (1999–2007)	2001.5 (1999–2004)
End study period (year, IQR)	2012.5 (2011–2016)	2012 (2009–2015)	2011 (2006–2015)	2009.5 (2006–2013)	2003.5 (2002–2005)
Study type					
Cohort	15 (88)	9 (90)	21 (81)	14 (78)	0 (0)
Prospective	5 (29)	2 (20)	18 (69)	12 (66)	0 (0)
Retrospective	10 (58)	7 (70)	2 (8)	1 (6)	0 (0)
Not specified	0 (0)	0 (0)	1 (4)	1 (6)	0 (0)
Case-control study	2 (12)	1 (10)	5 (19)	4 (22)	2 (100)
Type of definition of IFI					
Ascioglu et al. ⁷	1 (6)	1 (10)	9 (35)	7 (39)	0 (0)
De Pauw et al. ⁸	12 (70)	7 (70)	14 (54)	10 (55)	1 (50)
Donnelly et al. ⁹	4 (24)	2 (20)	0 (0)	0 (0)	0 (0)
Other definition or not specified	0 (0)	0 (0)	3 (11)	1 (6) ^a	1 (50)
Continent					
North America	6 (35)	4 (40)	2 (8)	2 (11)	1 (50)
Asia	2 (12)	1 (10)	6 (23)	4 (22)	0 (0)
Europe	9 (53)	5 (50)	17 (65)	11 (61)	1 (50)
South America	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oceania	0 (0)	0 (0)	1 (4)	1 (6)	0 (0)
Centers					
Single-center	14 (82)	9 (90)	20 (77)	14 (78)	2 (100)
Multicenter	3 (18)	1 (10)	6 (23)	4 (22)	0 (0)
Population					
Adults	11 (65)	7 (70)	17 (65)	11 (61)	2 (100)
Adults and children	5 (35)	3 (30)	9 (35)	7 (39)	0 (0)
Type of hematological malignancies					
Hematological malignancy, any type	4 (23)	2 (20)	4 (13)	1 (6)	2 (100)
Lymphoproliferative disorder	0 (0)	0 (0)	2 (7)	0 (0)	0 (0)
Myeloid malignancy	4 (23)	2 (20)	4 (13)	3 (16)	0 (0)
Other ^b	1 (6)	1 (10)	2 (7)	2 (11)	0 (0)
Type of HSCT					
HSCT, any type	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Allo-HSCT	8 (48)	5 (50)	14 (55)	12 (67)	0 (0)
Auto-HSCT	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Funding source					
Institutional	5 (29)	2 (20)	9 (35)	6 (33)	0 (0)
Industry	1 (6)	1 (10)	2 (8)	2 (11)	0 (0)
Institutional and industry	2 (13)	2 (20)	2 (8)	1 (6)	0 (0)
No specific funding	5 (29)	3 (30)	3 (11)	2 (11)	0 (0)
Not reported	4 (23)	2 (20)	10 (38)	7 (39)	2 (100)
Total number of episodes	13,822	9 534	135,776	4 614	77
Total number of IFI episodes	846	622	2 086	723	53

ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; HSCT, hematogenous stem cell transplant; IFI, invasive fungal infection; IMI, invasive mould infection; IQR, interquartile range; MDS, myelodysplastic syndrome.

^a Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America defined cases of proven, probable and/or possible invasive aspergillosis.¹⁹

^b in IMI n=1 acute leukemia and MDS in transformation, in aspergillosis n=1 acute leukemia and n=1 AML/ALL.

inclusion in the meta-analysis. For IMI, this represented 622 cases among 9534 episodes evaluating any type of IMI, with 9 out of 10 (90%) studies considered methodologically sound. For IA, 723 cases among 4614 episodes assessing specifically IA were included, with 16 out of 18 (89%) studies considered methodologically sound.

[Additional file 10](#) outlines the methods and variables used in adjustments.

Qualitative synthesis

Risk factors, along with their measure effects and 95%CI for each study, are listed in [additional file 11](#). Among the variables that could not be pooled in meta-analyses, pulmonary comorbidity was significantly associated with both IMI and IA in three of four studies studying hematological malignancies (2 for IA and 1 for IMI) with OR ranging from 1.67 [95%CI 1.37–2.05] to 5.96 [95%CI 2.31–15.33].^{20–22} A history of IFI was significantly associated with IMI in two studies on hematological malignancies, reporting an HR of 5.55 [95%CI 2.14–14.41] and an OR of 5.17 [95%CI 2.89–9.25].^{23,24} Monocytopenia was also statistically

associated with IMI in multivariate analysis in one study on allo-HSCT patients, with an HR of 1.8 [95%CI 1.3–2.6].²⁵ Respiratory viral infections – including influenza, parainfluenza, lower respiratory tract infections and COVID-19 – were significantly associated with increased risk of IMI and IA, with reported HRs of 2.5 [95%CI 1.1–5.8] and 2.6 [95%CI 1.6–4.3] for IMI and 4.3 [95%CI 2.0–9.4] for IA, and an OR of 2.45 [95%CI 1.92–3.13] for IA, respectively.^{20,25,26} Additionally, high-exposure professions and house renovations were both significantly associated with IMI, with ORs of 3.43 [95%CI 1.52–7.7] and 4.01 [95%CI 1.89–8.52] in a study on AML patients.²¹

Three studies reported risk factors according to specific time periods following HSCT – one on any type of IMI and 2 on IA^{25,27,28} – though no risk factors from these could be pooled in meta-analyses ([additional files 12–14](#)).

Quantitative synthesis

Older age, studied exclusively in allo-HSCT recipients but for one study in the AML population, was significantly associated with

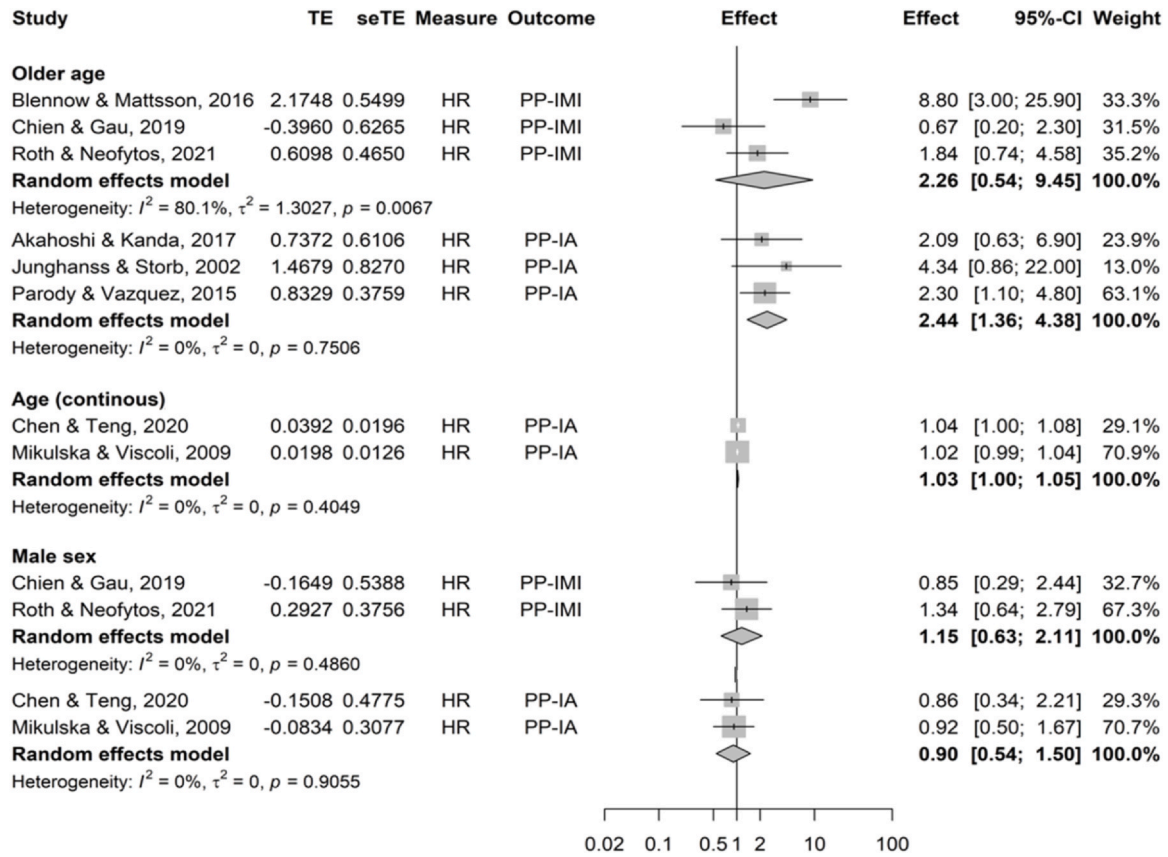


Fig. 2. Forest plot of patients' characteristics evaluated as risk factors for proven and/or probable invasive mould infections or invasive aspergillosis. CI, confidence interval; HR, hazard ratio; IA, invasive aspergillosis; IMI, invasive mould infection; PP, proven and/or probable; seTE, standard error of treatment effect; TE, treatment effect.

proven and/or probable IA (pooled HR = 2.44 [95%CI 1.36–4.38], 3 studies) (Fig. 2, see additional file 15 for studies including possible infections).

Relapsed and/or refractory hemopathy, studied across a wide variety of hematological settings (hematological malignancies, AML/MDS patients, allo-HSCT recipients), was significantly associated with an increased risk of both IMI and IA (Fig. 3, additional file 16). When restricting the analysis to proven and/or probable infections,

the association with IMI yielded a pooled HR of 3.43 [95%CI 1.58–7.46] (I^2 37.6%, $p_{het} = 0.20$, 2 studies). For IA, the association was supported by a pooled HR of 3.44 [95%CI 1.87–6.34] and a pooled OR of 10.00 [95%CI 1.09–92.02] (2 studies each). However, this last result showed substantial heterogeneity ($I^2 = 87.8\%$, $p_{het} = 0.0042$) (Fig. 3). Results pooled for the 3 studies focusing on AML/MDS patients gave consistent results (pooled HR 3.25 [95%CI 1.89–5.60]) (additional file 17).

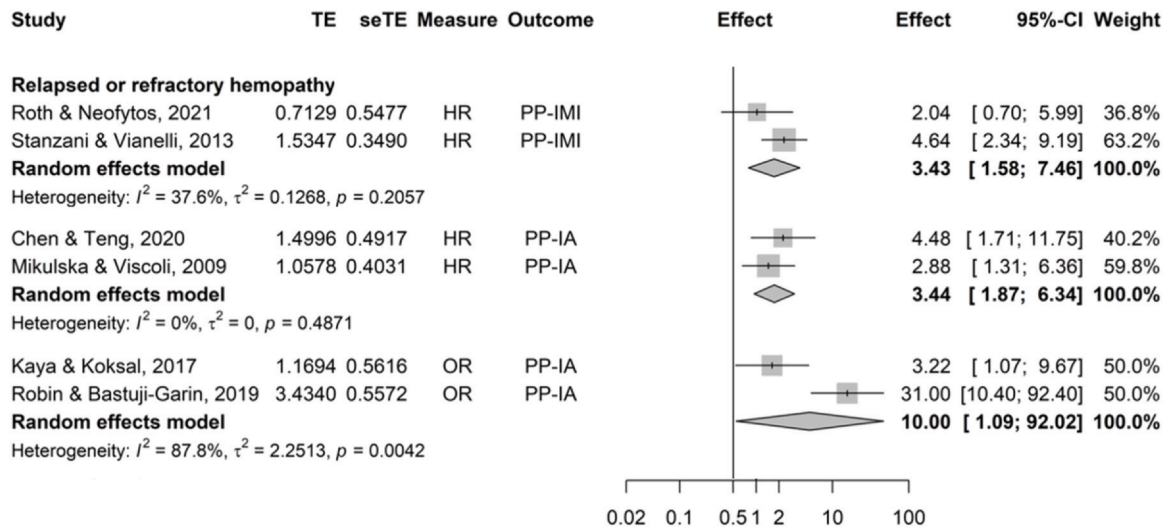


Fig. 3. Forest plot of hemopathy characteristics evaluated as risk factors for proven and/or probable invasive mould infections or invasive aspergillosis. CI, confidence interval; HR, hazard ratio; IA, invasive aspergillosis; IMI, invasive mould infection; OR, odds-ratio; PP, proven and/or probable; seTE, standard error of treatment effect; TE, treatment effect.

Allo-HSCT at high-risk for mortality (defined in each study with consensus definitions^{29,30}) was significantly associated with IMI (pooled HR with 2 studies 3.19 [95%CI 1.50–6.77]) (Fig. 4).

Both acute and chronic GvHD were significant post-transplant factors for IMI and IA (Fig. 4, additional file 18). For proven and/or probable infections, acute GvHD was associated with a pooled HR of 3.23 [95%CI 2.20–4.74] for IMI and 2.98 [95%CI 1.62–5.48] for IA, based on 4 studies each. Chronic GvHD was similarly associated with increased risk, with pooled HRs from 2 studies each of 2.95 [95%CI 1.25–6.96] for IMI and 3.84 [95%CI 1.74–8.52] for IA (Fig. 4).

Regarding biological parameters, CMV disease post-allo-HSCT and prolonged neutropenia were significantly associated with IA (pooled HR = 3.23 [95%CI 1.00–10.43] from 4 studies, with substantial heterogeneity ($I^2 = 83.5\%$, $p_{het} = 0.0004$) and pooled OR = 4.85 [95%CI 2.15–10.97], 2 studies) (Fig. 5, see additional file 19 for studies including possible cases). When restricting to the 2 studies in the allo-HSCT population, prolonged neutropenia remained statistically significant (pooled HR 2.55 [1.02–6.39], $I^2 = 23.6\%$, $p_{het} = 0.25$) (additional file 20). Lymphopenia was significantly associated with IMI (pooled HR = 1.77 [95%CI 1.03–3.03], 2 studies) (Fig. 5).

Regarding treatments, corticosteroid use studied in allo-HSCT recipients, regardless of the dose, was associated with IA (high dose: pooled HR = 4.67 [95%CI 2.79–7.82], 5 studies, low dose: pooled HR = 2.31 [95%CI 1.19–4.46], 2 studies) whereas it was not significantly

associated with IMI in patients with hematological malignancies (pooled OR = 1.72 [95%CI 0.74–4.00], 2 studies) (Fig. 6). Antifungal prophylaxis demonstrated a protective effect against IA when evaluated using OR (pooled OR = 0.19 [95%CI 0.07–0.52], 2 studies). However, this protective effect was not observed when using HRs (pooled HR = 1.02 [95%CI 0.33–3.08], 2 studies) (Fig. 6, see additional file 21 for studies including possible cases). Similar results were found when restricting to acute leukemia patients (pooled OR 0.87 [95%CI 0.43–1.78], 2 studies and pooled HR 0.21 [95%CI 0.009–0.52], 3 studies) (additional file 22).

Sensitivity analyses and quality of evidence

Sensitivity analyses excluding studies methodologically relatively poor (additional files 23–32), pediatric population (additional files 33–36) or episode-based studies (additional files 37–41) yielded consistent results when pooling was feasible.

Quality of evidence is displayed in additional file 42. The associations between relapsed/refractory hemopathy, allo-HSCT at high-risk for mortality, acute and/or chronic GvHD, neutropenia, lymphopenia, CMV disease or high dose corticosteroids and IMI/IA have a low level of evidence whereas the associations between older age, prolonged neutropenia, low dose corticosteroids or antifungal prophylaxis and IMI/IA have a very low level of evidence.

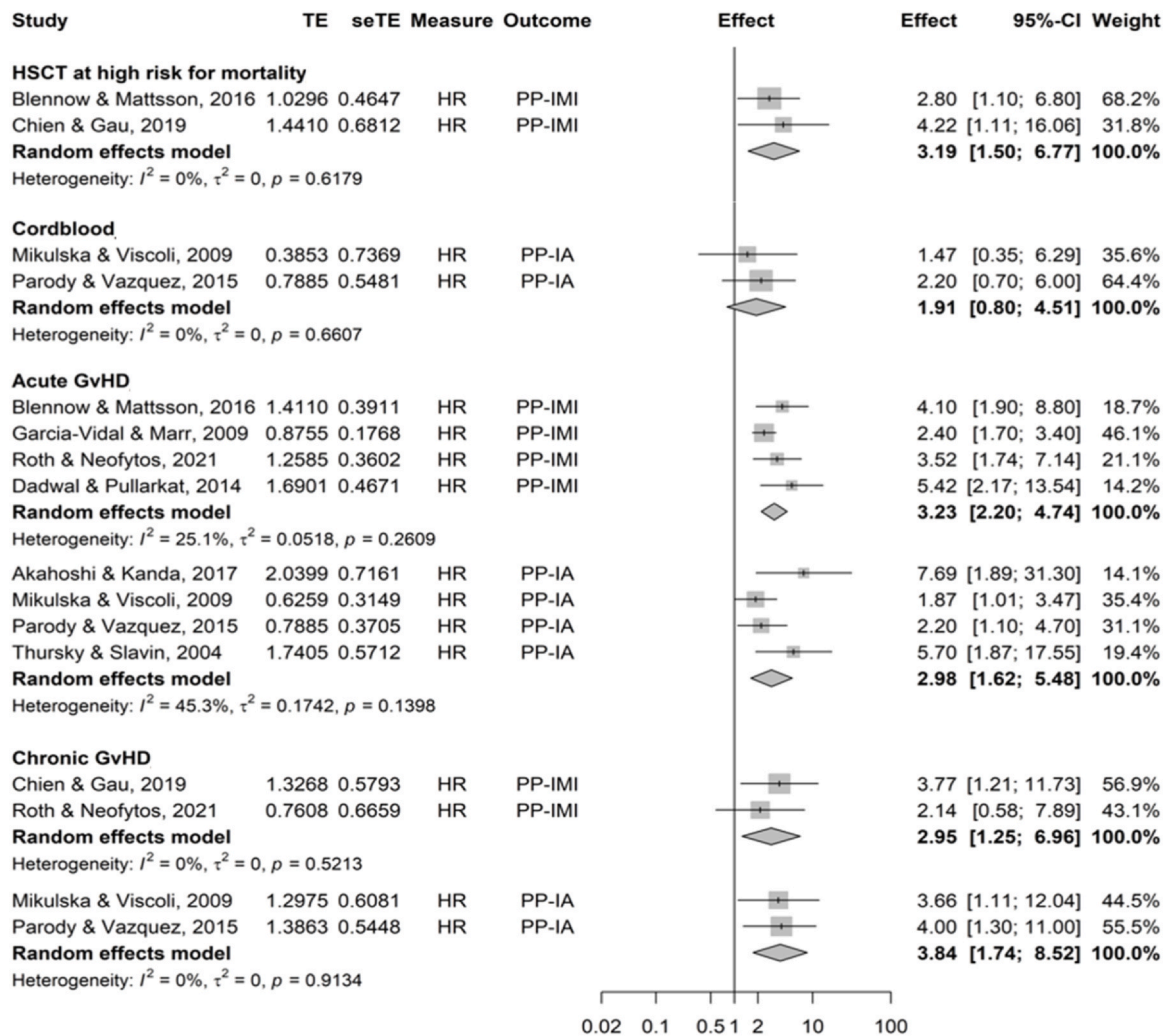


Fig. 4. Forest plot of hematogenous stem cell transplantation status' characteristics evaluated as risk factors for proven and/or probable invasive mould infections or invasive aspergillosis. CI, confidence interval; GvHD, graft versus host disease; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IA, invasive aspergillosis; IMI, invasive mould infection; PP, proven and/or probable; seTE, standard error of treatment effect; TE, treatment effect.

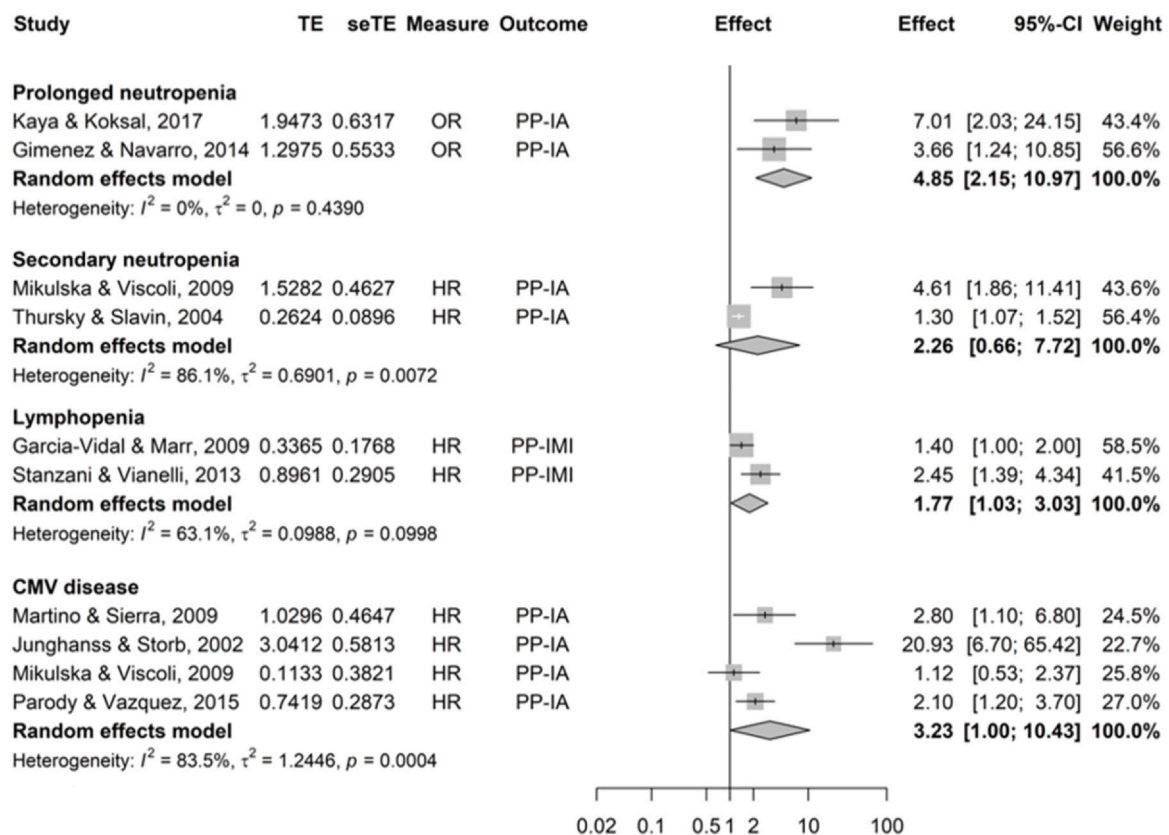


Fig. 5. Forest plot of biological parameters evaluated as risk factors for proven and/or probable invasive mould infections or invasive aspergillosis. CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio; IA, invasive aspergillosis; IMI, invasive mould infection; OR, odds-ratio; PP, proven and/or probable; seTE, standard error of treatment effect; TE, treatment effect.

Discussion

In this meta-analysis, relapsed/refractory hematological malignancies, including when restricting to the AML/MDS population, as well as both acute and chronic GvHD were associated with an increased risk of both IMI and IA. Allo-HSCT at high-risk for mortality and lymphopenia was associated with IMI. Conversely, in studies focusing specifically on IA, prolonged neutropenia, including when studied exclusively in the allo-HSCT population, CMV disease and corticosteroids use post-allo-HSCT – regardless of dosage – were significantly associated with this infection.

These findings reinforce previously reported associations between relapsed/refractory hematological malignancies and allo-HSCT at high for mortality and any type of IFI.³¹ Notably, in the prior meta-analysis, the association between relapsed/refractory disease and IFI risk was assessed exclusively in studies involving AML and myelodysplastic syndromes (MDS) patients. In contrast, the present study focuses exclusively on IA and IMI, and includes a broader hematological population with relapsed/refractory diseases – encompassing patients with hematological malignancies and allo-HSCT recipients. As a result, it extends the generalizability of this association to the wider hematological population at risk for IMI.

Acute and chronic GvHD, neutropenia and corticosteroid use may be interrelated factors associated with IMI/IA, especially in allo-HSCT. The risk persists both during the neutropenic and post-engraftment periods due to GvHD and subsequent corticosteroid therapy. Corticosteroids impair macrophage and neutrophil functions, crucial for killing inhaled *Aspergillus* spores and *Aspergillus* evolution into invasive hyphae.^{32–35} In this study, corticosteroid use was associated with IA but not with IMI overall, regardless of dosage. This may be attributed to differences in the studied populations: IMI cases primarily involved hematological malignancies and AML/MDS,

whereas IA studies focused solely on allo-HSCT recipients. Despite this distinction, corticosteroid doses did not differ significantly between groups. Determining a precise neutropenia duration threshold remains challenging, with cut-offs varying from 3 to 60 days across studies. Interestingly, our meta-analysis did not establish an association between post-engraftment secondary neutropenia and IMI/IA, possibly due to the dominant role of host inflammation in this period rather than hyphal proliferation and angioinvasion, as suggested by murine models.³⁶

Post-transplant CMV infection was associated with IMI/IA, aligning with prior findings on IFI of any type, as evidenced by a recent meta-analysis of 12 studies – half of which only included IMI or IA cases – reporting a pooled HR of 2.58 (95% CI 1.78– 3.74), $I^2 = 75\%$.³⁷ CMV and IMI share common risk factors such as GvHD, lymphopenia and corticosteroid use.^{38,39} Additionally, CMV compromises immune cells involved in fungal clearance and indicates a heavily immunosuppressed host state.^{40,41}

Our findings are consistent with current guidelines recommending the use of posaconazole prophylaxis for post-allo-HSCT patients receiving corticosteroids for acute GvHD.^{42,43} In our study, the protective effect of antifungal prophylaxis was observed in studies reporting ORs, but not in those using HRs. These discrepant results may reflect differences in the statistical models employed—namely, logistic regression versus Cox model. Nonetheless, additional prophylactic strategies may warrant consideration for allo-HSCT recipients at high-risk of mortality in the pre-engraftment period, as well as for individuals with relapsed or refractory hematological malignancies.

We applied a stringent methodology in this systematic review and meta-analysis. To ensure robust study comparisons between studies, we exclusively included research published after the introduction of standardized IFI definitions in 2002.^{7–9} This choice was

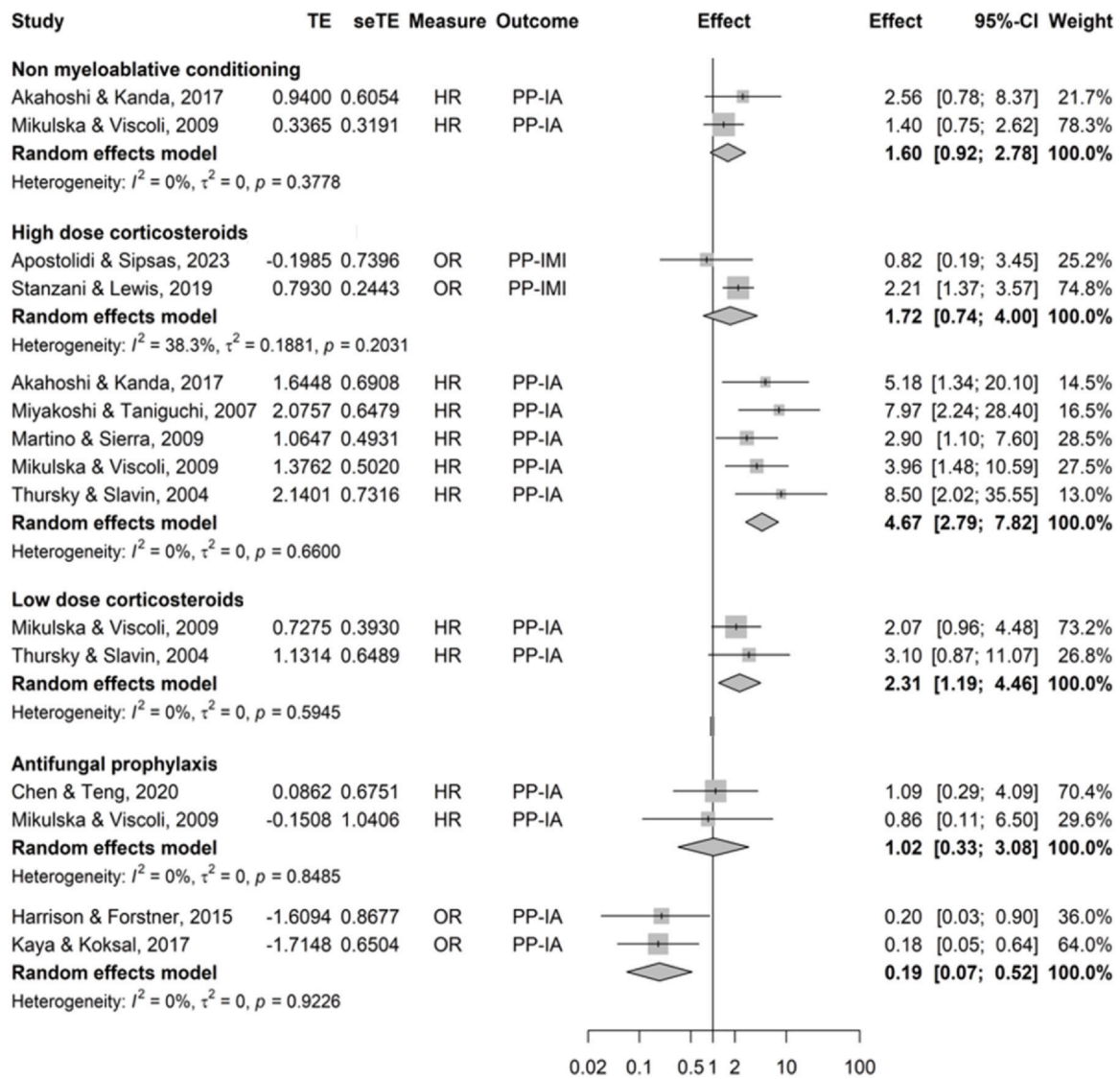


Fig. 6. Forest plot of treatment characteristics evaluated as risk factors for proven and/or probable invasive mould infections or invasive aspergillosis. CI, confidence interval; HR, hazard ratio; IA, invasive aspergillosis; IMI, invasive mould infection; OR, odds-ratio; PP, proven and/or probable; seTE, standard error of treatment effect; TE, treatment effect.

crucial, as a review published in 2001 found 173 studies reporting 485 different IFI definitions, demonstrating only fair overall agreement, which further declined when considering the degree of certainty of IFI.⁴⁴ Additionally, we performed two distinct analyses—one solely examining proven and/or probable IMI/IA and another incorporating possible cases based on the 2002 and 2008 EORTC/MSG definitions—to ensure greater confidence in the identified associations while reflecting the likelihood of underdiagnosed infections in the era before widespread use of advanced diagnostic methods. Despite these strengths, our study has limitations. Although the systematic review encompassed a large number of patients and studies, few variables were eligible for meta-analysis. Certain risk factors displayed considerable heterogeneity, which was amplified by the diverse confounding factors accounted for in each study. As a result, the overall quality of evidence ranged from low to very low. Furthermore, this study highlights the scarcity of data on mucormycosis in hematological patients.

In conclusion, physicians should remain vigilant for IMI in hematological patients, particularly those with relapsed/refractory diseases, allo-HSCT at high-risk of mortality, and acute and chronic GvHD. Additional risk factors including CMV disease and

corticosteroid use in the allo-HSCT population, neutropenia and lymphopenia appear to further heighten susceptibility to these severe infections. While current antifungal prophylaxis guidelines cover many at-risk groups, it might be worth considering expanding these recommendations to relapsed/refractory hematological malignancies, HSCT at high for mortality and CMV disease in the allo-HSCT population. Further research is necessary to better understand risk factors for mucormycosis in this population.

Author contributions

EG, AD, PMG, LA, LS, KL, FL, CGV, EB and JG designed the study. EG, LA and PMG selected the studies to be included in the systematic review and extracted the data from the studies. EG performed the statistical analysis. EG wrote the first draft with input from LS and AD. All authors contributed to the interpretation of the data, revised the draft critically for important intellectual content and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability

The authors will make the data available upon reasonable request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: C.G.-V. has received honoraria for talks on behalf of Gilead Sciences, MSD, Pfizer, Jansen, Novartis, Basilea, GSK, Shionogi, AbbVie and Advanz Pharma, and grant support from Gilead Sciences, Pfizer, GSK, MSD and PharmaMar. KL has received honoraria and grant support outside of the topic of this manuscript by Gilead, MSD and ViiV Healthcare. All other authors do not declare any conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jinf.2025.106574](https://doi.org/10.1016/j.jinf.2025.106574).

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