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Systematic review

Risk factors for invasive fungal infections after haematopoietic stem cell transplantation: a systematic review and meta-analysis

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ABSTRACT

Background: Invasive fungal infections (IFIs) are common infectious complications after haematopoietic stem cell transplantation (HSCT), seriously threatening the survival of patients.
Objectives: This systematic review aimed to investigate risk factors associated with IFIs following HSCT.
Methods: Two authors independently conducted the selection of studies and extraction of data. Risk factors for IFIs, invasive aspergillosis or invasive mould infections and invasive candida infection after HSCT were compiled separately by meta-analysis using RevMan 5.4 and R language 4.1.2.
Data sources: Pubmed, EMBASE, Web of Science, and the Cochrane Library until April 2023.
Study eligibility criteria: Case-control or cohort studies that assessed risk factors for IFIs among HSCT recipients were included.
Participants: Patients experiencing HSCT.
Test/s: None.
Reference standard: The IFIs were defined according to the European Organisation for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria, or a similar definition.
Assessment of risk of bias: A modified version of the Newcastle-Ottawa Scale was used.
Methods of data synthesis: A random-effects model with the Mantel-Haenszel method was used to pool results from primary studies.
Results: Out of 1637 studies screened, 51 studies involving 109 155 patients were included, with 45 studies providing adequate data for meta-analysis. Identified risk factors for IFIs included prolonged neutropenia, intensified therapy for graft-versus-host disease (GVHD), previous transplantation, previous proven or probable IFI, acute GVHD $\geq$ grade II, extensive or severe chronic GVHD, use of anti-thymocyte globulin during transplantation, haploidentical transplantation, high-dose glucocorticoids, Epstein-Barr virus infection, cytomegalovirus infection or reactivation, and lower albumin. Conversely, antifungal prophylaxis emerged as the sole preventive factor. For invasive aspergillosis or invasive mould infections, the top risk factors were extensive or severe chronic GVHD, respiratory viral infection, high-dose glucocorticoids, acute GVHD $\geq$ grade II, and human leukocyte antigen mismatch. Cord blood transplantation was the sole significant risk factor for invasive candidiasis. However, there was likely a high degree of interdependence among various risk factors.
Discussion: This meta-analysis provides a thorough review of risk factors for IFIs infection after HSCT. The achieved insights can aid in stratifying patients who are at an elevated risk of IFIs and promoting antifungal preventive strategies. **Li Biyun, Clin Microbiol Infect 2024;30:601**

Introduction

Invasive fungal infections (IFIs) are an important complication in patients undergoing haematopoietic stem cell transplantation (HSCT). The 1-year mortality rate in patients diagnosed with IFIs after HSCT ranged between 36.0% and 72.0% [1]. Diagnosing IFIs remains challenging, particularly in the early stages of transplantation and in patients with critical conditions [2]. Various guidelines across different countries advocate for the implementation of primary antifungal prophylaxis (PAP) during the posttransplant neutropenic phase and in the presence of graft-versus-host disease (GVHD) [1,3,4]. However, with the widespread use of

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antifungal prophylaxis among HSCT recipients, several drawbacks have emerged over the recent years, such as the occurrence of side effects and the emergence of resistance [5,6]. Therefore, precise identification of risk factors for IFIs is essential for the management of invasive fungal disease (IFD) after transplantation.

Previous clinical studies have assessed the risk factors for developing IFIs. Risk factors are typically derived from retrospective studies analysing and identifying different risk factors [7]. However, there is still a lack of systematic evaluation of risk factors for all IFIs and specific fungal infections. Our research aims to improve our understanding of the risk factors for IFIs after HSCT.

Materials and methods

Protocol and registration

This study has been registered in PROSPERO database (Registration No. CRD42023415199).

Search strategy

We searched Pubmed, EMBASE, Web of Science, and the Cochrane Library from inception to April 2023. The search string is described in the Supplementary Appendix (Table S1). The reference lists from the included studies and reviews were screened to identify potentially relevant articles.

Eligibility criteria

Cohort and case-control studies that evaluated any risk factors for IFIs in HSCT recipients were assessed. The IFIs were defined according to the European Organisation for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria [8–10], or a similar definition. To control for any confounding effects, only studies that performed multivariable-adjusted analysis were included in the systematic review and meta-analysis. The criteria for exclusion and determination of duplicates are presented in Fig. 1 and Table S2. Specific types of adjustment analyses are given in Table S3.

Data extraction

Two investigators (B-Y Li and Y-H Han) independently reviewed and extracted data in duplicate, using a standard process for each retrieved article. Discrepancies regarding study eligibility or data extraction were resolved by consensus, after obtaining the opinion of a third author (Y-F Li). The following information was collected from each study: the first author's name, year of publication, study setting (single-centre or multicentre), study design (case control or cohort), number of HSCT recipients, number of cases with IFIs, incidence of IFIs, time from transplantation to diagnosis of IFIs, and risk factors for the development of IFIs. The corresponding authors of the original studies were contacted when additional data were required. The risk factors previously reported in the literature were extracted according to defined criteria, including older age (age >40 years), prolonged neutropenia (ANC $<0.5 \times 109/L$, $\geq$10 days), and high-dose glucocorticoids ($\geq$1 mg/kg/day), etc. Specific definitions are presented in Appendix Table S6.

Quality assessment

B-Y Li and Y-H Han independently participated in the quality assessment, and disagreements were resolved by consulting with a third reviewer (Y-F Li) until consensus could be attained. The Newcastle-Ottawa Quality Assessment Scale, which is based on a star rating system, was used to assess the quality of each individual observational study [11]. A score of 7–9 points was indicative of high-quality research, whereas a score of 0–3 points was representative of low-quality research.

For each risk factor, we used the Grading of Recommendations Assessment, Development and Evaluation approach to appraising the certainty (quality) of direct and indirect evidence and the network estimate for all outcomes [12]. Two reviewers (B-Y Li and Y-H Han) independently assessed the certainty of evidence using the following criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias. We summarized the certainty of evidence as high, moderate, low, or very low.

Statistical analysis

Meta-analysis was performed for risk factors where at least two studies analysed the potential association with the occurrence of IFIs, and the definition of such factors was consistent across studies. The generic inverse variance method, assigning weights based on study variance, was employed to combine risk estimates and associated 95% CIs from individual studies. Heterogeneity between studies was evaluated using Cochran's Q-test and quantified by the I^2 statistic, with values < 25%, 25%–75%, and >75% interpreted as low, moderate, and high levels of heterogeneity, respectively. A random-effects model with the Mantel-Haenszel method was used to pool results from primary studies. Publication bias was assessed through funnel plots and the Egger's regression test. Statistical analysis and figure generation were conducted using Review Manager 5.4 software from the Cochrane Collaboration and R 4.1.2 programming language.

Results

Characteristics of included studies

Overall, 1637 studies were retrieved from the primary search (Fig. 1). After applying eligibility criteria, 51 studies that enrolled 109 155 patients were included and 45 studies provided sufficient data for meta-analysis [13–63]. The vast majority of studies explored risk factors for allogeneic HSCT (n = 45, 88.2%), five articles addressed autologous and allogeneic HSCT, and one article assessed autologous HSCT only. Study designs included case-control studies (n = 5, 9.8%), retrospective cohort studies (n = 33, 64.7%), and prospective cohort studies (n = 13, 25.5%). Among them, there were 15 studies multicentre studies, while the remaining were single-centre studies.

The characteristics of the included studies are summarized in Table 1. Approximately half of the studies investigated risk factors for any IFIs (n = 25, 49.0%), more than one-third of the studies assessed invasive aspergillosis (IA) or invasive mould infections (IMIs) (n = 19, 37.2%), three studies concentrated on invasive Candida infections (ICI, 5.9%) and another four targeted other fungal infections. About half of the studies included only adult patients (n = 25, 49.0%), five studies investigated risk factors only in paediatric recipients, whereas the remaining studies included both adults and children or did not report patients' age. Antifungal prophylaxis after HSCT was used in the majority of studies (n = 44, 86.3%), of which the most commonly used drugs were triazoles, such as voriconazole, fluconazole or itraconazole. Few studies used secondary prevention (n = 5, 9.8%). In total, 25 risk factors were analysed. Supplements Table S6 and S7 describe the definitions used for each risk factor and IFIs across the included studies.

Risk factors for any IFIs in HSCT recipients

Incidence rates of IFIs ranged from 5.9% to 35.1% and the median onset of IFIs varied from 34 to 174 days following HSCT. Notably, 20

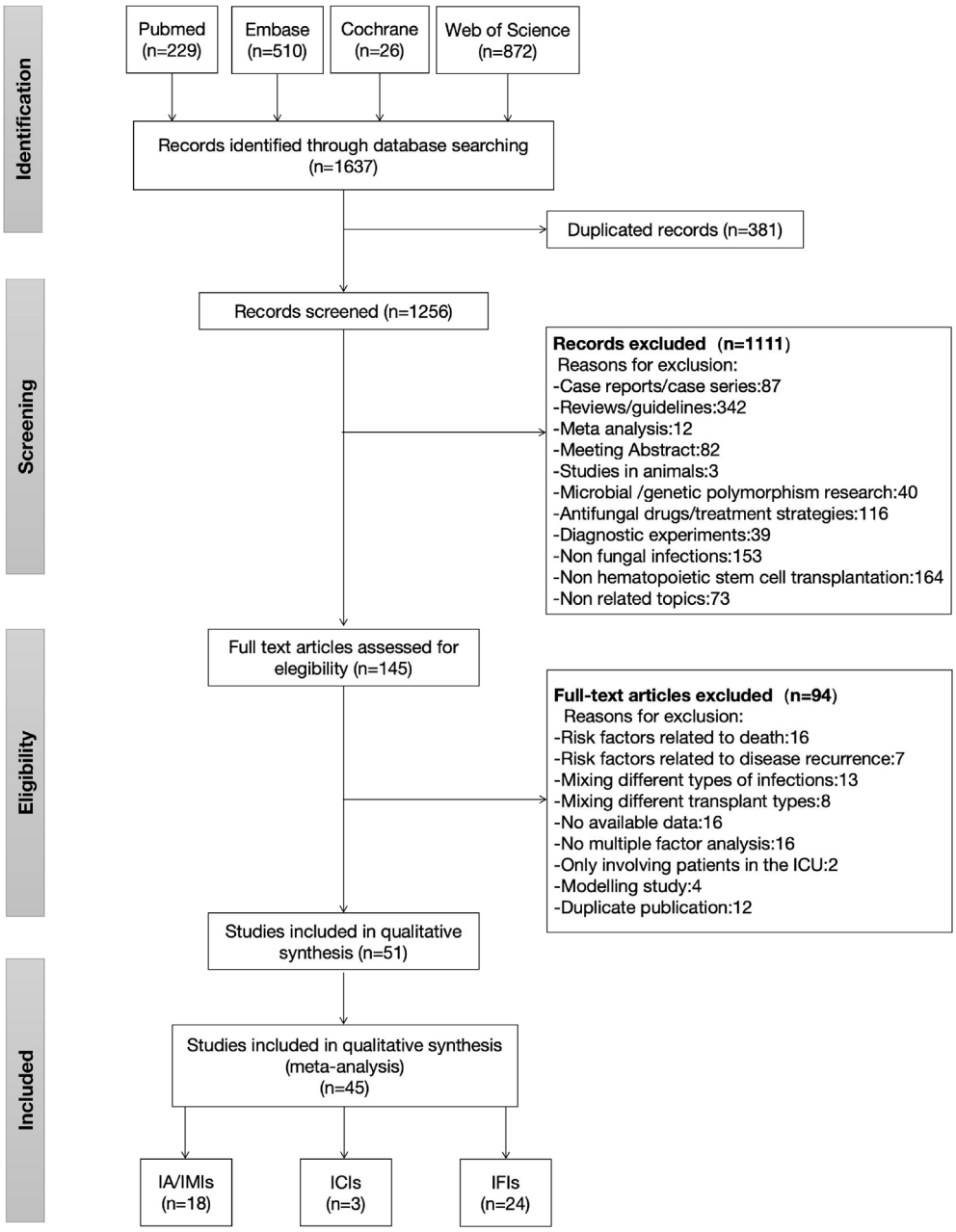

Fig. 1. PRISMA flow chart.

factors in 24 studies were analysed and 14 factors associated with any IFIs were identified. Separate meta-analyses were conducted for HRs and ORs based on the distinct original study statistical effect estimates. In the results pooled with HR as the effect estimate, the top five independent risk factors were prolonged neutropenia, the utilization of anti-thymocyte globulin (ATG), previous transplantation, extensive or severe chronic GVHD, and acute GVHD $\geq$ grade II. For OR as the effect estimate, the most relevant five risk factors were unrelated donor transplantation, prolonged neutropenia, haploidentical transplantation, previous proven or probable IFD and intensified GVHD therapy. Due to the inclusion of different risk factors explored in the original studies, the pooled results for different effect estimates were inconsistent. However, prolonged neutropenia, previous proven or probable IFD, and haploidentical transplantation were significant in all analyses. Antifungal prophylaxis was the only preventive factor for IFIs in this transplant population (OR, 0.38; 95% CI, 0.22–0.63; $p < 0.001$) (Table 2 and Fig. S1). The meta-analyses of individual risk factors are presented in Figs. S1.1–1.5.

Risk factors for IA/IMIs in HSCT

We analysed 18 studies assessing IA or IMIs, of which 12 studies analysed risk factors for IA only. We analysed 15 factors and found 10 factors strongly associated with IA or IMIs (Table 3 and Fig. S2). In the results pooled with HR as the effect estimate, the independent risk factors for IA or IMIs were extensive or severe chronic GVHD, high-dose glucocorticoids, respiratory viral infection,

Table 1
Characteristics of the included studies

Study	Study design	Unicentre/ multicentre; site	Study time frame	Study population	No. of patients	Control patients	Outcome	Antifungal prophylaxis	Median F/U period (months)[a]	Median onset of IFI (day)[b]	Incidence of IFI[b]	Quality assessment
Atalla 2015 [13]	Prospective cohort	Multicentre eight centres in Brazil	2007.5–2009.7	Adults and children	345	28	PP-IMIs	Fluconazole or Voriconazole or Itraconazole or Intravenous amphotericin B	NA	NA	8.1%	High
Blennow 2016 [14]	Retrospective cohort	Unicentre in Sweden	2001.1–2012.9	Adults and children	797	40	PP-IMIs	Nonabsorbable amphotericin B or fluconazole	19.2	NA	5.0%	High
Busca 2022 [15]	Retrospective cohort	Unicentre in Italy	2004.1–2020.12	Adults	563	58	PP-IFIs	PAP: Fluconazole, Micafungin, mould-active drugs; SAP	80.4	98.4	10.3%	High
Cesaro 2018 [16]	Retrospective cohort	Multicentre:153 centres in 26 European countries	2000.1–2012.12	Adults and children	28 542	347	PP-ICIs	Fluconazole or liposomal amphotericin B, echinocandins and triazoles	67.2	22	1.2%	High
Chien 2019 [17]	Retrospective cohort	Unicentre in China	2003.1–2014.12	Adults	245	17	PP-IMIs	Azoles or Echinocandins	16.6	385	6.9%	High
Choi 2017 [18]	Retrospective cohort	Multicentre in Korea	2013.01–2016.6	Adults	521	71	PP-IFIs	PAP: Micafungin, Itraconazole, Fluconazole; SAP	NA	NA	13.6%	High
Christen 2019 [19]	Retrospective cohort	Unicentre in Germany	2002.5–2011.8	Adults	290	26	PP-IFIs	Fluconazole, Voriconazole, Posaconazole	19.3	117	9.0%	High
Corzo-León 2015 [20]	Case control	Unicentre in the United States	2002.1–2011.4	Adults	378	53	PP-IFIs	Fluconazole or Voriconazole or Caspofungin	NA	147	14%	High
Fukuda 2003 [21]	Retrospective cohort	Unicentre in the United States	1997.12–2001.10	Adults and children	163	25	PP-IMIs	amphotericin formulation or itraconazole or voriconazole or caspofungin	23.9	107	15.3%	High
Gao 2016 [22]	Prospective cohort	Multicentre: 35 centres in China	2011.1.1–2011.10.30	Adults and children	818	63	PP-IFIs	PAP: Fluconazole, Itraconazole, Voriconazole, Caspofungin, Amphotericin B	NA	45	7.7 %	High
Garcia-Vidal 2008 [23]	Case control	Unicentre in the United States	1998.1.1–2002.12.31	Adults	1248	163	PP-IMIs	Fluconazole or amphotericin B	NA	NA	13.1%	High
Gil 2009 [24]	Prospective cohort	Unicentre in Poland	2005.1–2007.9	Adults	109	9	PP-IA	Fluconazole	NA	NA	8.3%	Moderate
Girmenia 2014 [25]	Prospective cohort	Multicentre:30 centres in Italy	2008.1.1–2010.12.31	Adults and children	1858	164	PP-IFIs	PAP:Fluconazole or mould-active drugs; SAP	NA	NA	8.8%	High
Harrison 2015 [26]	Retrospective cohort	Unicentre in Austria	2009.1–2013.12	Adults	242	25	PP-IFIs	Fluconazole or Voriconazole or Posaconazole	NA	NA	10.3%	High
Hazar 2019 [27]	Retrospective cohort	Multicentre:13 centres in Turkey	2014.1.1–2014.12.31	children	408	26	PP-IFIs	Fluconazole	NA	39.5	6.4%	High
Hol 2014 [28]	Retrospective cohort	Unicentre in The Netherlands	2004.1.1–2012.7.31	children	209	25	PP-IFIs	Fluconazole or Voriconazole, liposomal amphotericin B, caspofungin, posaconazole	27.9	34	12.0%	High
Hung 2012 [29]	Retrospective cohort	Unicentre in China	2000.1–2009.12	Adults	326	20	PP-IFIs	Azoles or echinocandins	NA	NA	6.1%	High
Junghanss 2002 [30]	Case control	Multicentre:2 centres in the United States	1997.12–2000.4	Adults	56	4	PP-IA	Fluconazole or amphotericin B	12.7	78	7.1%	Moderate
Kimura 2021 [31]	Retrospective cohort	Multicentre in Japan	2006 – 2017	Adults	21 015	582	PP-IA	NA	55.7	95	2.8%	High
Kimura 2022 [32]	Retrospective cohort	Multicentre in Japan	2009–2019	Adults and children	26 236	469	PP-ICIs	NA	45.4	29	1.8%	High
Labbé 2007 [33]	Prospective cohort	Unicentre in Canada	2000.7–2006.6	Adults	125	13	PP-IA	No routine antifungal prophylaxis	24	229	10.4%	High
Li 2012 [34]	Retrospective cohort	Unicentre in China	2000.1.1–2007.12.31	Adults and children	190	20	PP-IMIs	Fluconazole or itraconazole	21.8	124	12.8%	High
Little 2022 [35]	Retrospective cohort	Unicentre in the United States	2011.5–2021.5	Adults	210	19	PP-IYI	No routine antifungal prophylaxis	NA	28	9.0%	High
Liu 2016 [36]	Retrospective cohort	Unicentre in China	2002.1–2013.12	Adults	421	31	PP-IFIs	Fluconazole or echinocandins	14.8	139	7.4%	High
Ma 2020 [37]	Retrospective cohort	Unicentre in China	2016–2018	Adults and children	233	41	PP-IFIs	Voriconazole, itraconazole, caspofungin, micafungin	NA	NA	17.6%	High
Martino 2002 [38]	Retrospective cohort	Unicentre in Spain	1996–2000	Adults	395	37	PP-Non-Candida IFIs	Fluconazole, itraconazole, Amphotericin B	NA	27	9.4%	High

Martino 2009 [39]	Prospective cohort	Unicentre in Spain	1999–2007	Adults	219	27	PP-IA	No routine antifungal prophylaxis	NA	218	12.3%	High
Marzuttini 2021 [40]	Retrospective cohort	Unicentre in Italy	2016.1–2019.8	NA	118	6	ICIs	PAP: micafungin; SAP: liposomal amphotericin B,	NA	26	5.1%	Moderate
Mihu 2008 [41]	Prospective cohort	Unicentre in the United States	1999.1.1–2003.12.31	Adults and children	398	22	PP-IA	Fluconazole、voriconazole、micafungin	NA	164	6%	Moderate
Mikulska 2009 [42]	Prospective cohort	Unicentre in Italy	1999.1.1–2006.12.31	Adults	306	45	PP-IA	Fluconazole or Amphotericin B or Voriconazole	9.5	45	14.7%	High
Miyakoshi 2007 [43]	Retrospective cohort	Unicentre in Japan	2002.3–2005.11	Adults	128	13	PP-IA	Fluconazole or micafungin	20.9	20	10.20%	High
Montesinos 2015 [44]	Retrospective cohort	Unicentre in Spain	2001.1–2013.3	Adults	404	57	PP-IFIs	PAP: Fluconazole or itraconazole or Voriconazole	22	NA	14%	High
Morrison 1994 [45]	Prospective cohort	Unicentre in the United States	1974–1989	Adults and children	1186	123	PP-Non-Candida IFIs	Nystatin or clotrimazole, amphotericm B	NA	25	10%	Moderate
Omer 2013 [46]	Retrospective cohort	Unicentre in the United States	2000–2010	Adults	271	42	PP-IFIs	Fluconazole	16.3	174	15%	High
Ozyilmaz 2010 [47]	Retrospective cohort	Unicentre in Turkey	2003.11–2008.9	Adults	148	22	PP-IFIs	PAP: Fluconazole、SAP: Amphotericin B	12	76	14.90%	High
Parody 2014 [48]	Retrospective cohort	Multicentre:10 centres in Spain	1997.1.1–2009.3.31	Adults	434	68	PP-IA	Itraconazole or osaconazole or Voriconazole or Amphotericin or Fluconazole or echinocandins	51	170	15.70%	High
Post 2007 [49]	Retrospective cohort	Unicentre in Austria	2000.1–2003.12	Adults and children	104	23	PP-IA	Fluconazole, amphotericin B, voriconazole, caspofungin	NA	116	23%	Moderate
Riches 2016 [50]	Case control	Multicentre:66 centres in the United States	1995–2008	Adults and children	11 856	124	NAMI	Azoles, Amphotericin, echinocandins	61.5	48	NA	High
Robin 2019 [51]	Case control	Multicentre in France	2005–2010	Adults	651	185	PP-IA	Posaconazole	63.5	133	NA	High
Satwani 2009 [52]	Retrospective cohort	Unicentre in the United States	2001.1–2007.12	Children	86	13	IFIs	liposomal amphotericin B	27	160	15%	High
Shi 2015 [53]	Retrospective cohort	Unicentre in China	1998.11–2009.12	Adults and children	408	92	PP-IFIs	Fluconazole or itraconazole	28	140	22.5%	High
Srinivasan 2013 [54]	Prospective cohort	Unicentre in the United States	1990–2009	Children	759	115	PP-IFIs	Amphotericin or echinocandins or voriconazole	95.5	NA	15.20%	High
Styczyński 2021 [55]	Prospective cohort	Unicentre in Poland	2012–2019	Children	187	25	PP-IFIs	Fluconazole, Posaconazole, voriconazole	NA	66	13.4%	High
Sun 2013 [56]	Retrospective cohort	Unicentre in China	2007.1–2010.12	Adults and children	1042	61	PP-IFIs	Fluconazole, voriconazole, amphotericin B, itraconazole, caspofungin, micafungin	34.3	NA	5.9%	High
Sun 2015 [57]	Prospective cohort	Multicentre: 31 centres in China	2011.1.1–2011.10.30	Adults and children	1053	94	PP-IFIs	Triazoles	6	45	8.9%	High
Thursky 2004 [58]	Retrospective cohort	Unicentre in Australia	1991.1–1998.6	Adults	217	19	PP-IA	Fluconazole, itraconazole	11	72	8.80%	High
Van-Burik 2007 [59]	Prospective cohort	Multicentre: 15 centres in the United States	1995.3–2000.10	Adults and children	404	90	IFIs	NA	50.4	NA	22%	Moderate
Wald 1997 [60]	Retrospective cohort	Unicentre in the United States	1987.1.1–1993.6.30	Adults and children	2496	214	PP-IA	NA	NA	16	8.60%	High
Xu 2007 [61]	Retrospective cohort	Unicentre in China	2003.6–2004.9	Adults and children	148	52	PP-IFIs	Fluconazole	3	62	35.1%	High
Yong 2017 [62]	Retrospective cohort	Multicentre: 2 centres in Australia	2006.1–2010.12	Adults	419	38	PP-IFIs	Fluconazole, amphotericin B, itraconazole, posaconazole	36.5	76	9.10%	High
Zhang 2010 [63]	Retrospective cohort	Unicentre in China	2000.1–2007.12	Adults and children	286	55	PP-IFIs	Fluconazole	18.3	NA	19.80%	High

PP-IYI, proven or probable invasive yeast infection; PP-NAMI, proven or probable non-Aspergillus mould infection; PP-ICI, proven or probable invasive candida infection; PP-IMIs, proven or probable invasive mould infections; PP-IA, proven or probable invasive aspergillosis; PAP, primary antifungal prophylaxis; SAP, secondary antifungal prophylaxis; NA, not available.

[a] Convert the time of median follow-up period in the original literature to months.

[b] Data representing the corresponding fungal species explored by the research institute.

Table 2
Independent risk factors for any IFI

Risk factors	No. of studies[a]	Hazard ratios (HR)					Odds ratios (OR)				
		No. of studies[b]	No. of patients	HR (95% CI)	I^2%	p	No. of studies[b]	No. of patients	OR (95% CI)	P^2%	p
Male recipients	12	2	273	0.95 (0.53–1.71)	0	0.86					
Stem cell source: cord blood	6	2	357	1.54 (0.12–19.26)	79	0.74					
Donor											
Unrelated donor	11	4	2940	2.31 (0.98–5.46)	66	0.06	2	1871	4.13 (1.39–12.26)	63	0.01
HLA mismatch donor	7	3	2556	1.57 (0.74–3.30)	46	0.24					
Haploidentical transplantation	6	4	2397	2.09 (1.14–3.84)	47	0.02	2	1871	3.04 (1.04–8.86)	56	0.04
Type of conditioning: MAC	10	4	1084	1.25 (0.45–3.49)	63	0.67					
Previous transplantation	6	2	812	2.93 (1.67–5.17)	0	<0.001					
Previous proven/probable IFD	13	5	1527	2.65 (1.24,5.69)	44	0.01	3	1434	2.50 (1.03–6.04)	61	0.04
Graft-versus host disease											
Acute GVHD ≥ grade II	19	11	5754	2.67 (2.08–3.42)	0	<0.001					
Extensive/severe chronic GVHD	14	7	4652	2.74 (2.05–3.67)	0	<0.001					
Virus infection											
CMV infection/reactivation	16	9	3071	2.22 (1.61–3.07)	29	<0.001	2	1871	1.22 (0.82–1.81)	0	0.32
EBV infection	3						3	2104	1.69 (1.04–2.74)	0	0.03
Prolonged neutropenia	9	3	1333	3.59 (1.29–10.00)	76	0.01	3	2104	3.96 (1.96–8.00)	39	<0.001
Liver injury	2						2	1431	1.49 (0.50–4.44)	65	0.47
Renal impairment	2						2	1871	1.43 (0.83–2.45)	0	0.2
Decreased albumin	3						2	1871	1.56 (1.07–2.27)	0	0.02
Antifungal prophylaxis	3						2	1295	0.38 (0.22–0.63)	0	<0.001
Use of ATG during transplantation	7	3	969	3.05 (1.72–5.42)	0	<0.001					
High-dose glucocorticoids	10	3	1102	1.70 (1.06–2.72)	0	0.03					
Intensified GVHD therapy	2						2	1295	2.39 (1.36–4.19)	0	0.002

ATG, anti-thymocyte globulin; CMV, cytomegalovirus; EBV, epstein-barr; GVHD, graft-versus-host disease; MAC, myeloablative conditioning virus.
[a] The number of studies where the risk factor was considered in the univariate analysis.
[b] The number of studies included in the meta-analysis.

Table 3
Independent risk factors for IA/IMI

Risk factors	No. of studies[a]	Hazard ratios (HR)					Odds ratios (OR)				
		No. of studies[b]	No. of patients	HR (95% CI)	I^2%	p	No. of studies[b]	No. of patients	OR (95% CI)	I^2%	p
Age >40 y	9	5	24 489	1.98 (1.32–2.97)	38	<0.001					
Male recipients	12	5	3767	1.31 (0.80–2.14)	36	0.28					
Underlying disease: lymphoma	2	2	470	2.74 (0.30–24.76)	84	0.37					
Stem cell source: Cord blood	3	2	740	1.93 (0.85–4.41)	0	0.12					
Unrelated donor	9	3	2845	1.98 (1.01–3.87)	0	0.0469					
HLA mismatch	10	4	4395	2.07 (1.47–2.96)	0	<0.001					
Type of conditioning: MAC	8	2	410	0.19 (0.01–2.96)	93	0.23					
Acute GVHD ≥ grade II	13	9	26 711	2.62 (2.27–3.02)	0	<0.001					
Extensive/severe chronic GVHD	6	3	903	3.81 (1.96–7.43)	0	<0.001					
CMV infection/reactivation	14	10	23 670	3.09 (1.64–5.82)	89	<0.001	2	841	2.57 (0.76–8.73)	80	0.13
Respiratory viral infection	2	2	1467	3.18 (1.91–5.30)	0	<0.001					
Secondary neutropenia	4	2	433	2.03 (0.70–5.92)	79	0.19	2	841	2.62 (0.83, 8.27)	72	0.1
Prolonged neutropenia	4	2	229	1.34 (1.05, 1.72)	0	0.02					
HCT-CI ≥ 3	3	2	21 812	1.78 (1.13–2.80)	34	0.01					
High-dose glucocorticoids	10	5	4396	3.37 (2.39–4.77)	0	<0.001					

ATG, anti-thymocyte globulin; CMV, cytomegalovirus; EBV, epstein-barr virus; GVHD, graft-versus-host disease; HCT-CI, haematopoietic cell transplantation comorbidity index; MAC, myeloablative conditioning.
[a] The number of studies where the risk factor was considered in the univariate analysis.
[b] The number of studies included in the meta-analysis.

cytomegalovirus (CMV) infection or reactivation, acute GVHD ≥ grade II, HLA mismatch, age >40 years, unrelated donor, HCT-CI ≥3, and prolonged neutropenia. For OR as the effect estimate, only two risk factors, CMV infection or reactivation and secondary neutropenia, were included in the meta-analysis and neither showed significance. The meta-analyses of risk factors are presented in Figs. S2.1-2.4.

Risk factors for invasive candida infection in HSCT

In this study, three studies assessing ICI were analysed, and cord blood transplantation (HR, 2.28; 95% CI, 1.51–3.44; p < 0.001) was the only significant risk factor (Table 4 and Fig. S3). The meta-analyses of risk factors are presented in Fig. S3.1.

Certainty of evidence

Methodological quality assessment according to the Newcastle-Ottawa Quality Assessment Scale indicated that all the studies scored ≥5 stars, suggesting moderate-to-high quality studies (Table S4). Table S8 demonstrates the certainty of the evidence for each risk factor. All predictors were of moderate and high quality, except for CMV infection or reactivation, unrelated donor

Table 4
Independent risk factors for invasive Candida infection

Risk factors	No. of studies[a]	Hazard ratios (HR)				
		No. of studies[b]	No. of patients	HR (95% CI)	I^2%	p
Male recipients	3	3	54 896	0.94 (0.53–3.44)	87	0.85
Stem cell source: cord blood	2	2	54 778	2.28 (1.51–3.44)	47	<0.001

[a] The number of studies where the risk factor was considered in the univariate analysis.
[b] The number of studies included in the meta-analysis.

transplantation, myeloablative conditioning (MAC) and intensified GVHD therapy, which were scored as low-quality evidence.

Evaluation of publication bias

The assessment of publication bias or other small study bias for the factors, which were included in more than seven studies in the analysis, was assessed through funnel plots and Egger's regression test. Funnel plots for acute GVHD ≥ grade II, extensive or severe chronic GVHD, and CMV infection or reactivation are illustrated in Fig. S4. None of the funnel plots shown above have significant asymmetry.

Discussion

This is the first systematic review and meta-analysis assessing risk factors for IFIs after HSCT. It is noteworthy that 51 articles that investigated the risk factors for IFIs after HSCT were identified. Apart from confirming the widely recognized risk factors (e.g. older age, HLA mismatch, persistent neutropenia, GVHD, CMV infection, utilization of glucocorticoids, and cord blood transplantation) [64,65], the present meta-analysis also identified respiratory viral infection, EBV infection, previous transplantation, and the use of ATG during transplantation. The present study demonstrated that various factors were associated with IA or IMIs after HSCT, and the most relevant independent risk factors included extensive or severe chronic GVHD, respiratory viral infection, high-dose glucocorticoids, CMV infection or reactivation, acute GVHD ≥ grade II, and prolonged neutropenia. Cord blood transplantation was an independent risk factor for ICI.

Almost all risk factors significantly associated with IFIs after HSCT have biological plausibility. Several significant risk factors in this study were mainly related to the patient's treatment and complications after transplantation. Among all the identified risk factors, prolonged neutropenia after transplantation was found as the most crucial predictor of IFIs and one of the predictors of IA or IMIs. This association has been reported consistently from five studies of any IFIs and one study of IA [18,37,44,49,53,57]. Secondary neutropenia after engraftment is also an important risk factor for the development of IA. Mikulska et al. [42] considered both delayed neutrophil engraftment and secondary neutropenia as strong predictors of IA. Morrison et al. [45] demonstrated that delayed engraftment could be a risk factor for non-Candida IFIs. Notably, neutrophils have long been regarded as a key cell population for host defence against Aspergillus because they may play a direct role in the destruction of hyphae and in prevention of conidia germination [66,67]. The use of haematopoietic factors, such as granulocyte colony-stimulating factor, shortens the duration of neutropenia and reduces the incidence of IFI [68,69]. However, the studies included in this systematic review did not consider haematopoietic factors as risk or protective factors, and further studies are therefore required to confirm the relationship between the utilization of haematopoietic factors and IFI after transplantation.

Extensive or severe chronic GVHD after transplantation was noted as the most important independent risk factor associated with IA. The onset of chronic GVHD tended to be related inversely to the degree of histocompatibility. This might be related to both neutrophil dysfunction and to the recently recognized importance of cellular immunity [66,70]. In this meta-analysis, the majority of the included study explored the effect of acute or chronic GVHD as a risk factor, and the results revealed that acute GVHD ≥ grade II and extensive or severe chronic GVHD were risk factors for IFIs, including IA or IMIs, which supports the current evidence that recommends antifungal prophylaxis for this population.

Two studies [42,51] on adult recipients reported recurrence of underlying diseases as a risk factor for IA. The study by Mikulska et al. [42] concluded that pretransplant disease recurrence was also a risk factor for IA. However, due to the small number of studies, this factor was not analysed in the present meta-analysis. Research has shown that the tumour microenvironment caused by leukaemia relapse after transplantation could cause damage to the function of natural killer cells. The natural killer cells can be activated by various fungal components and kills fungi directly by secreting cytotoxic molecules [71]. Relapse may affect the reconstruction of immune function after transplantation, increasing the incidence of infections [72,73].

Respiratory viral infection and CMV infection or reactivation were also significant risk factors for IA or IMIs. Respiratory viruses, for instance, may render individuals more susceptible to fungal coinfections by causing damage to the airways and impairing neutrophil function [74]. Rhinovirus and other respiratory viruses may increasingly be recognized as risk factors for IFIs as multiplex polymerase chain reaction assay for viral detection is becoming more widely available [75]. The present meta-analysis showed that CMV infection or reactivation and EBV infection were risk factors for IFIs in the transplant population. Morrison et al. [45] reported CMV infection also as a significant risk factor for nonCandida fungal infections. The CMV has an immunomodulatory effect that impairs host innate and cell-mediated immunity, playing an essential role in the development of IFIs [76]. A meta-analysis on the association between CMV infection and IFIs in recipients of allogeneic HSCT indicated that CMV infection after transplantation increased the risk of IFIs, which is consistent with the findings of the present meta-analysis [77].

In this meta-analysis, high-dose glucocorticoids, and intensive treatment of GVHD were risk factors for IFIs. Irreversible damage of the skin, liver, and gastrointestinal tract, and loss of barrier integrity damaged the innate immune function, and the immunosuppressive drugs used to control GVHD could also lead to the decline of cellular and humoral immunity [78]. However, the treatment of intensive GVHD remarkably varies from study to study. Harrison et al. [26] and Labbé et al. [33] assessed the effect of using TNF-α inhibitors on the occurrence of IFIs, and one study [33] did not find any association. Further studies are essential to confirm the relationship between the use of TNF-a inhibitors and posttransplant IFI. The ATG treatment also reported significant results in the present meta-analysis, and it was found that the use of ATG in pretreatment regimens and other GVHD preventive strategies, such as BTK inhibitors and PI3K inhibitors, increased the risk of IFIs [29,79].

Donor-related factors such as haploidentical transplantation, unrelated donors, and HLA mismatch are also risk factors for IFIs. Compared with HLA-matched related donor transplants, transplant

recipients with these risk factors are more likely to experience severe GVHD and delayed immune reconstitution, increasing the risk for fungal infection [80]. Cord blood transplantation was the only significant independent risk factor for ICI in this meta-analysis. Compared with the traditional source of transplantation, the infectious complications of cord blood transplantation have two characteristics: the relatively low number of haematopoietic progenitor cells and the limited number and immaturity of umbilical cord lymphocytes, which may lead to prolonged neutropenia after transplantation [81,82]. There are also some risk factors, such as glucocorticoids, acute GVHD, and HLA mismatch, which were significant in Kimura et al. [32], while they have not been included in our analysis. This is related to the lack of articles related to Candida, which is also the limitation of this study.

Antifungal prophylaxis was found as the only preventive factor of IFIs in the present meta-analysis. A network meta-analysis of 69 randomized controlled trials indicated that voriconazole could be the most appropriate antifungal for patients undergoing HSCT, whereas further studies are required to validate this finding [83].

There were also risk factors that did not exhibit significance, such as pretreatment regimens of different intensities and different primary haematological diseases. Post et al. [49] concluded that patients with reduced-intensity conditioning were at a higher risk of developing IA compared with MAC. Satwani et al. [52] reported the same conclusion related to IFIs. However, it has also been claimed that nonmyeloablative preconditioning may reduce the incidence of infection, and further research is still needed to assess these transplant strategies [84].

Our study has some limitations. First, the meta-analyses of certain risk factors demonstrated high heterogeneity, as observed in prolonged neutropenia ($I^2 = 76\%$, $p = 0.01$). This variability could stem from different definitions of neutropenia duration across studies. Second, the meta-analysis exclusively combined outcomes from multivariate analysis, a method that mitigates confounding bias, while it may also result in an overestimation of the significance of identified risk factors. To address this concern, a level of evidence certainty evaluation was conducted, considering the number of studies that assessed the risk factors through univariate analysis. Third, the investigation did not stratify risk factors according to the type of HSCT, distinguishing between allogeneic and autologous procedures. The inclusion of only one study investigating patients after autologous transplants limited the ability to explore potential differences. It is crucial to recognize that allogeneic HSCT may confer an increased risk of fungal disease development, given the slower immune reconstitution and higher incidence of fungal diseases postallogeneic HSCT compared with autologous HSCT [1,37]. Furthermore, dependencies between different risk factors are likely to be high and were not considered in the meta-analyses. Finally, only three studies related to ICI were included; some well-known risk factors could not be presented in the final meta-analysis.

Conclusion

In conclusion, this is the first systematic review and meta-analysis to compile risk factors for IFI in HSCT recipients. Most of the factors identified were associated with the host, prophylaxis and HSCT strategies and complications. According to the results of this study, patients in future studies can be stratified according to the number of risk factors associated with IFI. These data can be used to target antifungal preventive strategies.

Author contributions

B-Y Li and Y-H Han are co-first authors and drafted the manuscript. Conceptualization: B-Y Li and Dao wang; supervision: Dao wang; project administration: B-Y Li; formal analysis: B-Y Li, Y-H Han and Y-F Li; data curation: B-Y Li, Y-H Han, Y-F Li and X-F Guo; visualization: B-Y Li and Y-H Han; writing—original draft: B-Y Li and Y-H Han; writing—review and editing: B-Y Li, Y-H Han and Dao wang.

Transparency declaration

The authors declare having no conflict of interest related to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.01.005.

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