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REVIEW ARTICLE

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Incidence, risk factors and mortality of invasive pulmonary aspergillosis in patients with influenza: A systematic review and meta-analysis

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Abstract

Background: An increasing number of cases of invasive pulmonary aspergillosis (IPA) complicating influenza have been described. We performed a meta-analysis to estimate the incidence, risk factors and outcomes of IPA in patients with influenza.

Methods: A systematic search was conducted in the PubMed, EMBASE and Cochrane Library databases from their inception to 31 August 2021 for eligible studies. Data on the incidence and risk factors of and mortality due to IPA in influenza patients were pooled using a random-effects model. Sensitivity analyses restricted to severe influenza requiring intensive care unit (ICU) support and multiple subgroup analyses were performed.

Results: Fourteen studies involving 6024 hospitalised patients with influenza were included. IPA was estimated to occur in 10% of influenza patients, with a mortality rate of 52%. Similar incidence (11%) and mortality (54%) estimates for IPA were observed in the sensitivity analysis including severe cases requiring ICU support. Subgroup analysis by geographical location showed a similar IPA rate between European (10%) and non-European (11%) studies. The IPA rate in the subset of nine studies using the modified AspICU criteria was 13%. Most subgroup analyses showed ≥50% mortality in IPA patients. Several predictors for IPA susceptibility were identified, including male sex, smoking history, chronic lung disease, influenza A (H1N1), severe conditions

Shi, Shan and Xia contributed equally to this work.

requiring supportive therapy, corticosteroid use before admission, solid organ transplant and haematological malignancy.

Conclusions: The IPA is common in individuals with severe influenza, and the prognosis is particularly poor. Influenza patients, especially those with high-risk factors, should be thoroughly screened for IPA.

KEYWORDS
incidence, influenza, invasive pulmonary aspergillosis, meta-analysis, mortality, risk factors

1 | INTRODUCTION

Influenza is a common but serious threat to public health, with significant associated morbidity and mortality. In Europe, laboratory-confirmed influenza accounts for 33% of acute respiratory infections during the influenza season in medical care patients.[1] In the USA, an estimated 4.3–21 million medical visits and 14–81 thousand hospitalisations were attributed to influenza annually from 2010–2020.[2] Amongst hospitalised patients with influenza, approximately 15%–19% required intensive care unit (ICU) support.[3] Globally, more than 291 thousand influenza-related deaths are estimated to occur each year.[4]

Secondary infection is an important concern in the management of influenza. Bacterial coinfection, most frequently with *Streptococcus pneumoniae* and *Staphylococcus aureus*, has been well documented in patients with influenza.[5] Regarding fungal coinfection, the Infectious Diseases Society of America (IDSA) guidelines for the management of seasonal influenza, released in 2018, states that invasive fungal coinfection is rare in adults with influenza.[6] However, the Public Health England guidance for adults with seasonal influenza states that invasive aspergillosis, including invasive pulmonary aspergillosis (IPA), has been increasingly recognised as a complication of influenza.[7] In recent years, an increasing number of cases of influenza-associated pulmonary aspergillosis (IAPA) has been described, especially in ICU settings.[8–23] The incidence of IPA in patients with influenza has been reported to be more than 10% in numerous studies,[14–16,18,19,21,22] indicating that this condition is not uncommon in influenza populations. Thus, there is currently a gap in knowledge about the frequency of influenza-related IPA.

The prognosis of influenza patients with IPA is generally poor, with mortality rates ≥50%,[10,13-16,18-21] although accurate estimates based on sufficient sample sizes are lacking. A previous study identified IPA as an independent predictor of mortality in critically ill patients with influenza.[19] To help improve clinical outcomes, early identification of individuals at high risk for developing IPA is important and necessary. At present, only a limited number of variables, such as advanced age,[11] male sex[19] and systemic corticosteroid use[11,14,19] have been identified to be associated with an increased IPA rate. However, these findings were not sufficiently robust due to limited sample sizes and retrospective study designs.

Notably, in an international survey of mainly critical care physicians, 63% of respondents were unaware of or had not seen a patient with IPA related to influenza in the last 5 years.[24] Similarly, a survey in the USA reported that only 26% of infectious disease specialists were familiar with influenza-associated IPA and less than 10% frequently used galactomannan (GM) testing in influenza patients admitted to the ICU.[25] These survey findings reflect a lack awareness of influenza-associated IPA in clinical practice. Therefore, we conducted a comprehensive systematic review and meta-analysis to estimate the incidence, risk factors and clinical outcomes of IPA amongst patients with influenza.

2 | METHODS

This present study was registered with PROSPERO (CRD42021274990) and conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26]

2.1 | Literature search strategy

A comprehensive literature search was performed using the electronic PubMed, EMBASE and the Cochrane Library databases from their inception to 31 Aug 2021. The search terms included invasive pulmonary aspergillosis, aspergillus, aspergillosis, influenza and influenza-associated pulmonary aspergillosis. The search strategies are provided in detail in Table S1. No language restriction was applied. Review articles and references listed in each identified study were also screened to identify additional literature.

2.2 | Inclusion criteria and study selection

Two authors independently selected studies based on the following inclusion criteria: (1) the study populations were hospitalised patients with influenza, (2) the data for calculation of the incidence or risk factors of or mortality due to IPA were available, (3) the study design was a randomised controlled trial (RCT) or observational; and (4) the diagnostic criteria for IPA was clearly provided, including but not limited to the criteria established 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) in 2008[27] and 2020,[28] the AspICU criteria,[29] the modified AspICU criteria[19] and the novel criteria developed by Verweij et al.[30] Details of above diagnostic criteria are described in Table S2. Considering the lack of transparency in the diagnostic process and the high risk of misclassification, we did not include studies using International Classification of Diseases (ICD) codes to define IPA. The exclusion criteria were as follows: (1) age less than 18 years; (2) sample size of less than 50; (3) reviews, case reports and non-peer-reviewed studies including conference abstracts, letters and correspondences; or (4) duplicated studies. For studies enrolling overlapping populations, we included only the study with the largest sample size.

2.3 | Data extraction and quality assessment

Two authors independently extracted the data from the included studies, and discrepancies were resolved by discussion. The following data were extracted from the included studies: first author, publication year, study design, country or region, study period, sample size, age, sex, type (or subtype) of influenza, healthcare setting, number of IPA cases, diagnostic criteria of IPA, potential risk factors and mortality. We rated the quality of the included studies using version 2 of the Cochrane risk-of-bias tool[31] for RCTs and the Newcastle-Ottawa scale (NOS)[32] for observational studies.

2.4 | Statistical analysis

The pooled incidence and mortality rates of IPA in patients with influenza were calculated using double arcsine transformation, with 95% confidence intervals (CIs). Multiple subgroup analyses were performed based on geographical location (Europe vs. non-Europe), diagnostic criteria of IPA (the most commonly used criteria vs. other criteria), setting (mixed hospitalised patients vs. ICU patients), study design (single centre vs. multicentre), sample size (≥100 vs. <100), proportion of bronchoalveolar lavage (BAL) fluid GM testing performed (≥30% vs. <30%) and proportion of influenza A (≥80% vs. <80%). Pooled estimates for each potential risk factor were generated if data from at least three studies were available, and the risk ratios (RRs) with 95% CIs are presented. Because of the limited number of studies included in the analysis of each predictor, subgroup analyses were not performed.

Sensitivity analyses restricted to severe influenza requiring ICU support were performed. Heterogeneity was assessed by the χ^2 test and the I^2 statistic. $p < .10$ or $I^2 > 50\%$ indicated significant heterogeneity.[33] Since a priori heterogeneity was expected, we used a random-effects model in all the analyses. Publication bias was examined by Egger's test. A p-value <.05 was considered statistically significant. We performed all analyses using RevMan version 5.3 (the Cochrane Collaboration) and R statistical software 4.1.0 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Study selection

We initially identified 1623 records, and 1288 studies remained after duplicates were removed. After screening the titles and abstracts, 29 studies were selected for full-text review. Fifteen studies were excluded for the following reasons: studies contained duplicate patients ($n = 7$), studies were not peer-reviewed ($n = 4$), studies had no clear IPA diagnostic criteria or used ICD codes to define IPA ($n = 3$), and studies had sample sizes of less than 50 ($n = 1$). The remaining 14 studies[10–23] with 6024 patients were included in the current meta-analysis. The literature search process is summarised in Figure S1.

All studies were observational studies, except for one RCT.[21] The studies were conducted in Europe ($n = 7$),[10,12,17–19,21,22] Asia ($n = 6$)[11,13–16,23] and North America ($n = 1$).[20] The number of hospitalised patients with influenza per study ranged from 77 to 2901, with a median of 156. The mean or median ages of the patients reported in individual studies ranged from 52 to 65 years, and the proportions of males ranged from 50.6% to 69.3%. Across the included studies, 5255 (87.2%) included critically ill patients admitted to the ICU, and 5587 (93.1%) included patients infected with influenza A virus. The modified AspICU criteria was most commonly used to define IPA[10,11,13,14,16,18–22] (Table 1).

A total of 397 influenza patients were diagnosed with IPA. IPA cases predominantly occurred in males with a history of diabetes mellitus and chronic obstructive pulmonary disease (COPD). The proportion of immunocompromised patients with EORTC/MSG host factors was 24.2% (64/264), and the proportion of patients with typical radiological features, including cavities, halos and air-crescent signs was 23.4% (59/252). Positive culture, BAL fluid GM tests and serum GM tests were observed in 59.1% (166/281), 80.4% (176/219) and 50% (106/212) of the patients, respectively. The mean (or median) times between admission and diagnosis of IPA ranged from 2 to 7 days. Voriconazole was the most commonly used agent for initial antifungal therapy (Table 2 and Table S3).

Amongst the observational studies, the median NOS score was 6, ranging from 4 to 8. The included RCT in the meta-analysis was found to have a high risk of bias. A full assessment is presented in Table S4.

3.2 | Meta-analyses of the incidence of invasive pulmonary aspergillosis

Thirteen studies[10–12,14–23] involving 5868 hospitalised patients with influenza reported the incidence of IPA, ranging from 1.21% to 31.1%. Meta-analysis demonstrated that the pooled incidence of IPA was 10% (95% CI: 5%–16%). The sensitivity analysis limited to the patients admitted to the ICU ($n = 5164$) showed that the pooled IPA rate was 11% (95% CI: 6%–18%; Figure 1).

TABLE 1 Characteristics of the studies included in the meta-analysis

Study	Design	Study period	Country or region	Sample size	Age, years[a]	Male, %	ICU, %	Flu A, %	EORTC/MSG host factors, %	BAL fluid GM testing performed, n (%)	Diagnostic criteria of IPA	Incidence, n (%)
Bellelli 2020[10]	RS, SC	2019	Italy	77	56.5 (26.8–74.5)	50.6	22.1	62.3	0	NA	Modified AspICU	5 (6.49)
Chen 2020[11]	RS, MC	2018	China	693	61 (36–76)	66.5	25.4	100	0	184 (26.6)	Modified AspICU	21 (3.03)
Coste 2021[12]	RS, MC	2009–2018	France	524	60 (49–69)	62.8	100	78.4[c]	9.5	NA	AspICU	10 (1.91)
Duan 2021[13]	RS, SC	2018–2019	China	156	58.6 ± 16.5	68.6	47.4	97.4	0	NA	Modified AspICU	NA
Huang 2020[14]	RS, SC	2017–2019	China	132	NA	63.6	100	84.8	NA	NA	Modified AspICU	41 (31.1)
Ku 2017[15]	RS, SC	2015–2016	Taiwan	124	65.0[b]	62.1	100	70.2	NA	NA	Custom criteria	21 (16.9)
Lin 2021[16]	RS, SC	2017–2019	China	157	61 ± 15	59.2	100	83.4	NA	32 (20.4)	Modified AspICU	18 (11.5)
Martin-Loeches 2017[17]	PS, MC	2009–2015	Spain	2901	51.6 ± 15.9	58.8	100	100	NA	0 (0)	Custom criteria	35 (1.21)
Nyga 2020[18]	RS, MC	2010–2019	France	213	NA	NA	100	84.5	22.1	NA	Modified AspICU	35 (16.4)
Schauwvlieghe 2018[19]	RS, MC	2009–2016	Belgium and Netherlands	432	59 ± 15	55.6	100	82.2	27.1	137 (31.7)	Modified AspICU	83 (19.2)
Schwartz 2020[20]	RS, SC	2014–2019	Canada	111	56.1 ± 15.8	54.1	100	82.9	17.1	16 (14.4)	Modified AspICU	8 (7.21)
Vanderbeke 2021[21]	PS, MC	2017–2020	Belgium, Netherlands and France	88	61 ± 15	56.8	100	83.0	13.6	58 (65.9)	Modified AspICU	21 (23.9)
Waldeck 2020[22]	RS, MC	2017–2018	Switzerland	81	NA	53.1	100	45.7	19.8	25 (30.9)	Modified AspICU	9 (11.1)
Zou 2020[23]	RS, MC	2013–2018	China	335	57 (45–68)	69.3	67.2	100	NA	0 (0)	EORTC/MSG 2008	18 (5.37)

Abbreviations: BAL, bronchoalveolar lavage; 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; Flu, influenza; GM, galactomannan; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; MC, multicentre; PS, prospective study; RS, retrospective study; SC, single centre; NA, not available.

[a]Values are expressed as the mean ± standard deviation or median (interquartile range).

[b]Value are expressed as the mean.

[c]Influenza genotype was known in 499 cases.

TABLE 2 Characteristics of influenza patients with invasive pulmonary aspergillosis

Study	*N*	Age, years[a]	Male, %	EORTC/MSG host factor, %	Typical radiological features (n)[c]	No. of test performed[d]	No. of test positive[d]	Days between admission and diagnosis IPA[a]	Initial antifungal therapy (*n*)	Mortality, *n* (%)
Bellelli 2020[10]	5	59 (58–71)	60.0	0	NA	NA	1/0/3/1	NA	NA	5 (100)
Chen 2020[11]	21	67 (61–82)	85.7	0	Cavity (3)	4/21/17/15	2/6/14/5	6.4 ± 4.8	VOR (18) and C-TE (3)	9 (42.9)
Coste 2021[12]	10	NA	NA	50	NA	NA	0/10/3/3	3 (1–9)	VOR (10)[e]	3 (30.0)
Duan 2021[13]	72	58.1 ± 16.0	69.4	0	Cavity (3)	0/67/24/67	0/37/23/41	NA	NA	38 (52.8)
Huang 2020[14]	41	NA	80.5	NA	HS (8), cavity or ACS (13)	-/41/41/41	2/21/29/13	6 (2–11)	NA	24 (58.5)
Ku 2017[15]	21	63[b]	52.4	NA	None	0/-/-/-	0/8/1/19	NA	VOR (14)	14 (66.7)
Lin 2021[16]	18	66 ± 12	61.1	NA	Cavity (1)	-/-/-/18	-/22/-/-	NA	VOR (18)	10 (55.6)
Martin-Loeches 2017[17]	35	NA	NA	NA	HS or ACS (25)	NA	2/-/-/-	NA	NA	NA
Nyga 2020[18]	35	60 (54–67)	62.9	45.7	Cavity or ACS (6)	-/34/27/33	5/26/19/20	5 (2–7)	VOR (32), ISA (1) and AMB (1)[f]	20 (57.1)
Schauwvlieghe 2018[19]	83	60 ± 12	67.5	45.8	NA	-/80/76/31	16/50/67/20	3 (0–7)	VOR (61), ECH (2), C-TE (9) and AMB (4)	42 (50.6)
Schwartz 2020[20]	8	50.5 ± 10.3	62.5	12.5	NA	-/8/6/0	1/8/4/0	NA	VOR (2), C-TE (3) and AMB (1)[g]	4 (50.0)
Vanderbeke 2021[21]	21	61 ± 10	61.9	14.3	NA	-/21/20/19	0/10/15/5	2 (1–4)	VOR (10)[h], C-TE (7)[i], C-TEA (1) and POS (1)	13 (61.9)
Waldeck 2020[22]	9	58 (57–64)	66.7	11.1	None	-/9/8/6	1/8/5/2	7 (3–8)	NA	3 (33.3)
Zou 2020[23]	18	60.6 ± 12.7	66.7	NA	NA	NA	NA	NA	NA	4 (22.2)

Abbreviations: ACS, air-crescent sign; AMB, amphotericin B; C-TE, combination of a triazole and an echinocandin; C-TEA, combination of a triazole, an echinocandin and amphotericin B; ECH, echinocandin; 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; HS, halo sign; ISA isavuconazole; NA, not available; POS, posaconazole; VOR, voriconazole.

[a]Values are expressed as the mean ±standard deviation or median (interquartile range).

[b]Value are expressed as mean.

[c]Typical radiological features included cavity, halo and air-crescent signs.

[d]Values are expressed as histopathological test/culture/bronchoalveolar lavage fluid galactomannan test/serum galactomannan test.

[e]Two patients presented with severe adverse effects leading to a change in antifungal drugs.

[f]Two patients received sequential AmBisome therapy and six patients received sequential combined therapy.

[g]One patient received sequential voriconazole.

[h]One patient received sequential posaconazole, and one patient received sequential anidulafungin.

[i]One patient received sequential amphotericin B, and one patient received sequential combined therapy (posaconazole and amphotericin B).

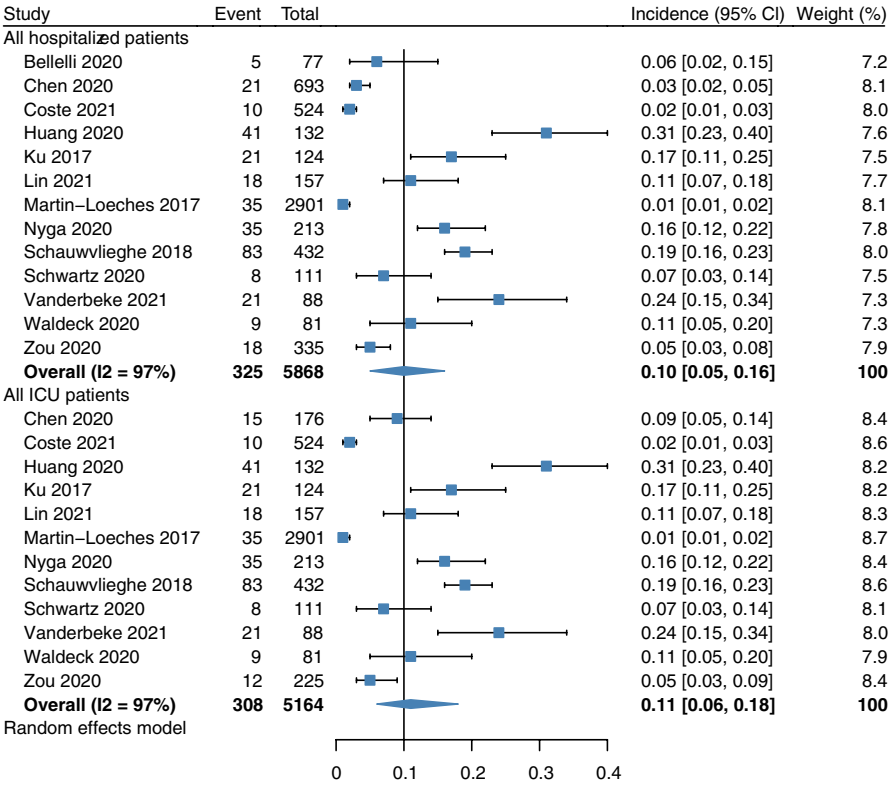

FIGURE 1 Forest plot of the incidence of invasive pulmonary aspergillosis in patients with influenza

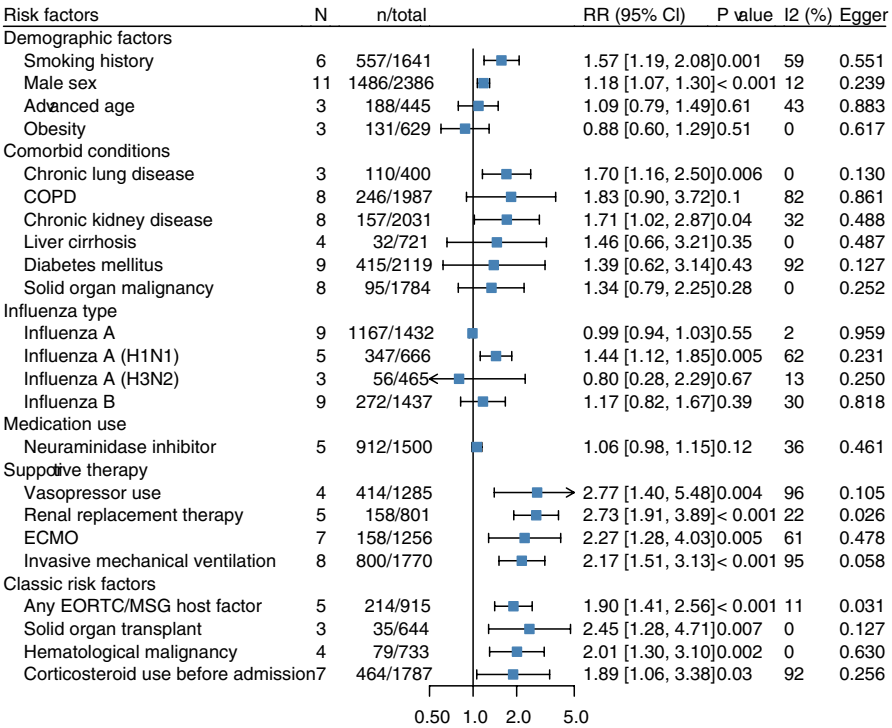

FIGURE 2 Forest plot of the risk factors for invasive pulmonary aspergillosis in patients with influenza

3.3 | Meta-analyses of risk factors for invasive pulmonary aspergillosis

Twenty-three potential risk factors for IPA amongst patients with influenza were evaluated in the present meta-analysis (Figure 2). Smoking history (RR: 1.57; 95% CI: 1.19–2.08; I^2 = 59%) and male sex (RR: 1.18; 95% CI: 1.07 to 1.30; I^2 = 12%) were associated with an increased risk of IPA. Patients with chronic lung disease (RR: 1.70; 95% CI: 1.16–2.50; I^2 = 0%) and chronic kidney disease (RR: 1.71; 95% CI: 1.02–2.87; I^2 = 32%) were more susceptible to IPA than those without. Influenza A subtype H1N1 was associated with an increased risk of the development of IPA (RR: 1.44; 95% CI: 1.12–1.85; I^2 = 62%). Supportive therapy, including vasopressor use (RR: 2.77; 95% CI: 1.40–5.48; I^2 = 96%), renal replacement therapy (RR: 2.73; 95% CI:

1.91–3.89; I^2 = 22%), extracorporeal membrane oxygenation (ECMO; RR: 2.27; 95% CI: 1.28–4.03; I^2 = 61%) and invasive mechanical ventilation (RR: 2.17; 95% CI: 1.51–3.13; I^2 = 95%), was applied more often in patients with IPA than in patients without IPA. Patients with any EORTC/MSG host factor had a 1.9-fold higher risk of IPA than patients without host factors (RR: 1.90; 95% CI: 1.41–2.56; I^2 = 11%). Solid organ transplant (RR: 2.45; 95% CI: 1.28–4.71; I^2 = 0%), haematological malignancy (RR: 2.01; 95% CI: 1.30 to 3.10; I^2 = 0%) and corticosteroid use before admission (RR: 1.89; 95% CI: 1.06–3.38; I^2 = 92%) were associated with an increase in the IPA rate. We found no significant relationship between IPA susceptibility and the following variables: advanced age, obesity, COPD, solid organ malignancy, diabetes mellitus, liver cirrhosis, neuraminidase inhibitor use and other types (or subtypes) of influenza. All individual forest plots and further details are provided in Tables S5-S27 and Figures S2-S24.

All the tested risk factors except chronic kidney disease showed consistent results in the sensitivity analyses. No significant relationship between IPA susceptibility and chronic kidney disease was observed in the sensitivity analysis of ICU patients (RR: 1.51; 95% CI: 0.83–2.75; I^2 = 42%; Table S28).

3.4 | Meta-analyses of mortality due to invasive pulmonary aspergillosis

Thirteen studies[10–16,18–23] reported mortality amongst influenza patients with IPA, with mortality rates ranging from 22.2% to 100%. Meta-analysis demonstrated that the pooled mortality of IPA was 52% (95% CI: 45%–60%; Figure 3). Influenza patients with IPA had a 2.4-fold higher risk of mortality than patients without IPA (RR: 2.40; 95% CI: 1.76–3.28; I^2 = 69%; Figure S25).

The sensitivity analysis limited to patients admitted to the ICU showed that the pooled mortality rate was 54% (95% CI: 48%-61%; Figure 3). Significantly higher mortality was observed in ICU patients with IPA than in ICU patients without IPA (RR: 2.23; 95% CI: 1.73–2.89; I^2 = 35%; Figure S26).

3.5 | Subgroup analyses and publication bias

Subgroup analyses based on location showed that the IPA rates in Europe (10%) and non-European regions (11%) were similar to those in the main analysis. A significantly higher IPA rate was observed in the subset of studies enrolling ICU patients exclusively (12%) compared with the subset of studies enrolling mixed hospitalised patients (4%). The incidence of IPA was significantly higher in studies using the modified AspICU criteria (13%) than in studies using other diagnostic criteria (5%). A significantly higher incidence of IPA was observed in the subset of studies in which ≥30% of patients underwent BAL fluid GM testing (18%) than in the subset of studies in which <30% of patients underwent BAL fluid GM testing (5%). Most subgroup analyses showed a ≥50% mortality rate (Table 3).

No significant publication bias was observed for any risk factor except the following: renal replacement therapy, invasive mechanical ventilation and any EORTC/MSG host factor (Figure 2).

4 | DISCUSSION

To our knowledge, this is the first meta-analysis to provide comprehensive insight into the incidence, risk factors and clinical outcomes of IPA amongst patients with influenza. Our meta-analysis estimated

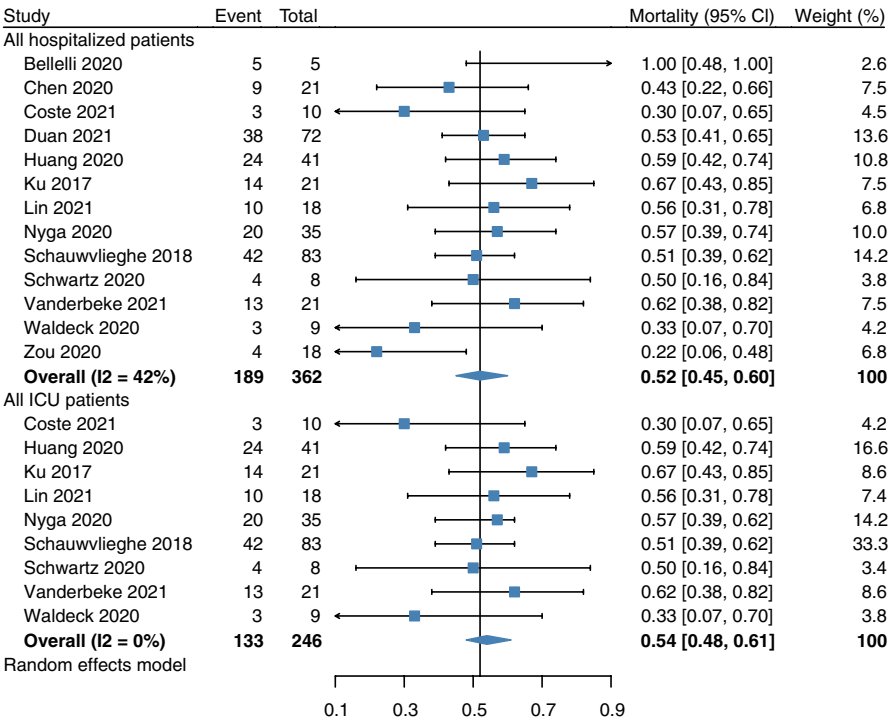

FIGURE 3 Forest plot of mortality due to invasive pulmonary aspergillosis in patients with influenza

TABLE 3 Subgroup analyses of the incidence and mortality rates of invasive pulmonary aspergillosis in patients with influenza

	Incidence				Mortality			
Subgroups	No. of studies	No. of patients with influenza	I^2, %	Proportion (95% CI)	No. of studies	No. of influenza patients with IPA	I^2, %	Proportion (95% CI)
Overall	13	5868	97	0.10 (0.05, 0.16)	13	362	42	0.52 (0.45, 0.60)
Location								
Europe	7	4316	98	0.10 (0.03, 0.19)	6	163	54	0.55 (0.40, 0.68)
Non-Europe	6	1552	95	0.11 (0.05, 0.19)	7	199	38	0.51 (0.41, 0.61)
Asia	5	1441	96	0.12 (0.04, 0.22)	6	191	49	0.51 (0.40, 0.62)
North America	1	111	NA	0.07 (0.03, 0.13)	1	8	NA	0.50 (0.15, 0.85)
Definition of IPA								
Modified AspICU	9	1984	95	0.13 (0.07, 0.21)	10	313	11	0.54 (0.48, 0.61)
Others	4	3884	95	0.05 (0.01, 0.10)	3	49	76	0.40 (0.13, 0.70)
Setting (study level)								
Included mixed hospitalised patients	3	1105	58	0.04 (0.02, 0.07)	4	116	78	0.51 (0.27, 0.75)
Included ICU patients exclusively	10	4763	98	0.12 (0.05, 0.21)	9	246	0	0.54 (0.48, 0.61)
Design								
Single centre	5	601	88	0.14 (0.07, 0.23)	6	165	29	0.60 (0.49, 0.70)
Multicentre	8	5267	98	0.08 (0.03, 0.15)	7	197	39	0.46 (0.36, 0.56)
Sample size (study level)								
≥100	10	5622	98	0.09 (0.05, 0.16)	10	327	24	0.51 (0.44, 0.58)
<100	3	246	81	0.13 (0.05, 0.24)	3	35	73	0.67 (0.29, 0.96)
Proportion of influenza A								
≥80%	9	5062	98	0.11 (0.05, 0.19)	9	317	13	0.52 (0.45, 0.58)
<80%	4	806	93	0.08 (0.02, 0.18)	4	45	73	0.59 (0.27, 0.87)
Proportion of BAL fluid GM testing performed								
≥30%	3	601	59	0.18 (0.12, 0.24)	3	113	0	0.51 (0.42, 0.61)
<30%	5	4195	94	0.05 (0.02, 0.09)	4	65	32	0.41 (0.26, 0.57)
Missing	5	1070	97	0.13 (0.03, 0.27)	6	184	48	0.59 (0.47, 0.70)

Abbreviations: BAL, bronchoalveolar lavage; CI, confidence interval; GM, galactomannan; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; NA, not available.

that the combined incidence of IPA in patients with influenza was 10%, with a pooled mortality rate of 52%. Several risk factors for the occurrence of IPA were identified, including male sex, smoking history, chronic lung disease, influenza A subtype H1N1, severe conditions requiring supportive therapy, corticosteroid use before admission, solid organ transplant and haematological malignancy.

The reported occurrence of IPA in influenza patients varied widely across studies, which may be partly explained by differences in illness severity. The subgroup analysis based on setting showed that the pooled IPA rate in the subset of studies enrolling only ICU patients was significantly higher than that in the subset of studies enrolling mixed hospitalised patients (12% vs. 4%), indicating that patients with severe influenza are more likely to develop IPA. Notably, the patients enrolled in the meta-analysis had mainly severe cases requiring ICU admission. We combined study data limited to severe influenza requiring ICU admission, and a similar IPA rate (11%) was observed. Therefore, our estimation of the IPA rate may be specific to the severe influenza population and not the mild influenza or general influenza population.

The diagnosis of IPA remains difficult, especially in influenza patients. Unlike patients with immunosuppression, most influenza patients with IPA showed no typical radiological features (eg classic halo or the air-crescent sign). Because influenza itself is not considered a classic host factor for IPA, the established EORTC/MSG criteria[27,28] are not suitable for influenza patients. To address this issue, a clinical algorithm (also known as AspICU criteria) was designed for critically ill patients.[29] The AspICU criteria includes an *Aspergillus*-positive lower respiratory tract specimen culture as an alternative criterion for host factors.[29] However, numerous studies have demonstrated that sensitivity of culture from lower respiratory tract specimen is not satisfactory.[34]In 2018, Schauwvlieghe et al.[19] further added GM testing of serum or BAL fluid to the mycological

criteria and proposed modified AspICU criteria to define IPA. More recently, a consensus case definition of IPA specific to influenza patients was developed by a panel of international experts.[30] Host factors are not necessary in the novel definition. Instead, an entry criterion, defined as a patient requiring ICU management for respiratory distress with a positive influenza test, was introduced.[30]

The IPA diagnostic criteria applied to influenza patients are variable, which may also impact the estimation of IPA occurrence. The modified AspICU criteria was the most commonly used across studies in the present meta-analysis. We conducted a subgroup analysis based on the definition of IPA, and a similar IPA rate was observed amongst the studies using the modified AspICU criteria (13%). At present, epidemiological data based on the latest definition of IPA are still limited. Moreover, differences in the application of BAL fluid GM testing and whether or not BAL fluid is performed as part of protocolised care for all ICU patients or only a subgroup of patients will heavily impact the incidence of IPA. Subgroup analysis showed the incidence of IPA was significantly higher in the subset of studies in which ≥30% of the patients underwent BAL fluid GM testing (18%) than in the sunsets of studies in which <30% of patients underwent BAL fluid GM testing (5%).

Geographical region may be an important factor affecting the reported IPA rate due to differences in climates, economies and health services. Nevertheless, the subgroup analysis showed a similar IPA rate between studies conducted in Europe (10%) and non-European regions (11%). Notably, the majority of the included studies were from Europe, followed by Asia. Studies from other regions are limited, which could be attributed to low awareness of influenza-associated IPA. An international survey demonstrated that 58% of participants in Europe were familiar with influenza-associated IPA, but the proportion outside Europe was only 39%.[24] We recommend that additional studies from other regions obtain accurate global estimates of the IPA rate in influenza patients.

The mechanisms that contribute to the high occurrence of IPA in influenza patients are not completely understood. Direct damage to the respiratory epithelium has been described in influenza,[35,36] which may facilitate *Aspergillus* spore penetration into the body. Neutrophils have been shown to play an important role in preventing the development of IPA.[37] A recent study showed that neutrophil recruitment was significantly induced by influenza through STAT1 signalling, which may partly explain why influenza hosts are susceptible to IPA.[38] Moreover, several factors might be involved in IPA susceptibility, such as alveolar macrophage dysfunction,[39,40] mucociliary clearance inhibition,[41] interleukin-10 overexpression,[42-44] T-helper cell differentiation dysregulation[9,45] and pulmonary microbiome alterations.[46]

Historically, IPA has been considered an opportunistic disease primarily affecting immunocompromised patients. Not surprisingly, we found that influenza patients with any EORTC/MSG host factors were at increased risk for IPA in the present meta-analysis. Specifically, we identified that both haematological malignancy and solid organ transplant were associated with increased IPA susceptibility. However, other host factors, such as neutropenia, T-cell immunosuppression and acute graft-versus-host disease, could not be validated in the meta-analysis due to the limited number of studies providing data on these variables.

It is well known that corticosteroid use can lead to susceptibility to opportunistic infection, primarily though damage to macrophages and neutrophil function.[47,48] A relationship between corticosteroid use and IPA has been well established in influenza patients,[11,14,19] and this is further supported by our findings. The significant heterogeneity in the pooled analysis of the effect of corticosteroid use on IPA susceptibility could probably be attributed to the large variations in corticosteroid dose and treatment course duration across the included studies. In influenza populations, a dose of greater than 0.1 mg/kg/day prednisone[19] and an accumulated corticosteroid dose greater than 200 mg[14] may be suitable predictors for the development of IPA. Notably, a considerably large number of patients received corticosteroid treatment in the included studies, although corticosteroids as adjunctive therapy for influenza are currently discouraged because of their correlation with hospital-acquired infection and an increased mortality rate.[49] Our findings suggest that corticosteroid treatment should be considered cautiously in influenza patients.

Influenza patients diagnosed with IPA were predominantly male. Our study showed that the incidence of IPA was significantly higher in males than in females, consistent with previous studies.[19] Several factors may explain the sex disparity in the IPA rate, including differences in exposure to sex hormones.[50] Influenza patients with a smoking history were more likely to develop IPA, which is consistent with the findings in non-selected populations.[51] Cigarette smoking may have an impact on the inhibition of mucociliary clearance and suppression of immunity, which makes patients who smoke more susceptible to IPA.

Three studies investigated the association between chronic lung disease and the incidence of IPA. The types of chronic lung diseases may have included asthma, COPD or other lung diseases, but the specific lung diseases of interest were not mentioned in these studies. Not surprisingly, we found that patients with chronic lung disease were more likely to develop IPA, as these populations commonly have impaired respiratory function and tend to use corticosteroids. COPD is one of the most frequently reported chronic lung diseases associated with increased IPA risk.[52] In an autopsy study, IPA was confirmed in 2.8% of patients, whilst as many as 44% of patients had COPD.[53] The present study showed a trend towards an increased IPA rate in patients with COPD compared with patients without COPD, although the difference did not reach statistical significance. Moreover, no significant associations between other underlying diseases (such as solid organ malignancy, diabetes mellitus and liver cirrhosis) and IPA susceptibility were observed in the present study.

Neuraminidase inhibitors (NIs), including oseltamivir, zanamivir and peramivir, are commonly used in the management of influenza. Several in-vivo studies demonstrated that neuraminidase plays an important role in the anti-*Aspergillus* immune response and that NIs may render patients vulnerable to IPA by blocking

neuraminidase.[54,55] However, ample evidence has demonstrated that early use of NIs could improve the prognosis of patients with influenza.[56,57] Recently, Seldeslachts et al.[58] established a double-hit mouse model and confirmed that the early use of oseltamivir could reduce the severity of influenza and decrease the risk of influenza-associated IPA. In the present meta-analysis, we did not identify an association between the use of NIs and IPA risk in influenza patients. This finding is difficult to interpret, as most of the included studies did not provide information about the timing of NI administration. Future studies should consider that the timing of NI treatment may affect the role of NIs in the development of influenza-associated IPA.

A previous study found that the severity of illness, as reflected by the acute physiology and chronic evaluation score, was positively related to the risk of IPA.[19] It is no surprise that patients with IPA were more likely to require vasopressor use, renal replacement therapy, ECMO and invasive mechanical ventilation than patients without IPA, as supportive therapy generally indicates a more severe condition.

Influenza was mainly caused by influenza A (H1N1 and H3N2) and influenza B viruses in the included studies. No significant difference in the risk for the development of IPA between influenza A and B groups was observed. However, we found that patients with influenza A subtype H1N1 had a 1.44-fold higher risk of IPA susceptibility than those with other types (or subtypes) of influenza. The reasons behind this interesting finding are still unclear. We observed that patients with influenza A (H1N1) were more likely to require ICU support than those with either influenza A (H3N2) or influenza B.[59-61] Therefore, it is plausible that influenza A (H1N1) may reflect more severe illness, which could partly explain the higher risk of IPA in this influenza subtype population. Our findings underline the important role of rapid identification of the influenza virus type, and individuals infected with influenza A subtype H1N1 should be monitored closely for the development of IPA.

Despite the antifungal use, IPA-associated mortality in influenza populations remains high. Our study demonstrated that the pooled IPA mortality rate was 52%. Moreover, patients with IPA had a nearly 2.4-fold higher risk of mortality than patients who did not develop IPA. Delayed IPA diagnosis may lead to a poor prognosis. Therefore, we recommend that severe influenza patients who have progressive features with a poor response to antibiotic therapy be screened as rapidly as possible for IPA. Once secondary IPA is confirmed, appropriate antifungal agents should be initiated immediately. However, early diagnosis alone is unlikely to substantially improve the outcome. In the study by Vanderbeke et al.[21] the mortality rate remained high despite early diagnosis and treatment. Therefore, other interventions (eg combination therapy or inhalation therapy) may be required to improve outcomes.

Considering the high probability of the development of IPA in influenza patients, primary prophylaxis may be considered in select populations with high-risk conditions. Unfortunately, partly due to the limited sample size, no apparent survival benefit was found in the recently published RCT evaluating posaconazole for the prevention of IPA in critically ill patients with influenza.[21] Nevertheless, the authors state that their findings support prompt initiation of empirical therapy with antifungal agents in influenza patients requiring ICU support and a timely mycological diagnostic work-up within 24–48 h.[21] Environmental controls, such as the installation of high-efficiency air filters, have been proposed to protect immunocompromised patients from exposure to *Aspergillus* spores.[62] However, the effect of these measures on the reduction in the IPA risk in influenza populations needs to be validated in the future studies.

The strength of the present meta-analysis is that it provides aggregate estimates of the incidence and risk factors of and mortality due to IPA in hospitalised patients with influenza. These findings can alert healthcare providers to consider the high frequency and poor outcomes of IPA in influenza patients. Several limitations of the current meta-analysis should be addressed. First, most of the included studies were retrospective, which increases the potential for bias. Second, most of the included studies were from Europe and Asia, making the generalisability of the conclusions limited. Additional studies from other regions are required to obtain more accurate global estimates. Third, although a total of 6024 hospitalised patients with influenza were included in the meta-analysis, the sample size within each analysis of potential risk factors was limited. To achieve a more comprehensive understanding of the predictors of IPA, additional large-scale studies are needed. Fourth, the incidence observed in this meta-analysis may underestimate the actual incidence of IPA. Indeed, it is likely that the implementation of a protocolised diagnosis strategy that includes BAL sampling and GM testing will increase the incidence. This was illustrated in the recent study by Vanderbeke et al.,[21] in which such a strategy resulted in a 24% incidence of IPA.

5 | CONCLUSION

Secondary IPA is common in patients admitted to the ICU for severe influenza and is associated with a high mortality rate. Special attention should be given to individuals with high-risk factors that predispose them to IPA, including male sex, smoking history, chronic lung disease, influenza A subtype H1N1, severe conditions requiring supportive therapy, corticosteroid use before admission, solid organ transplant and haematological malignancy.

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CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTION

Changcheng Shi: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Funding acquisition (lead); Methodology (equal); Software (lead); Writing – original draft (lead); Writing – review & editing (equal). **Qiyuan Shan:** Conceptualization (equal); Data curation (equal); Methodology (lead); Writing – review & editing (equal). **Junbo Xia:** Conceptualization (equal); Data curation (equal); Methodology (lead); Writing – review & editing (equal). **Liusheng Wang:** Data curation (supporting); Methodology (equal); Writing – review & editing (equal). **Linling Wang:** Formal analysis (supporting); Writing – review & editing (equal). **Lei Qiu:** Formal analysis (supporting); Writing – review & editing (equal). **Yaping Xie:** Formal analysis (supporting); Writing – review & editing (equal). **Nengming Lin:** Conceptualization (lead); Data curation (supporting); Project administration (lead); Writing – review & editing (lead). **Limin Wang:** Conceptualization (lead); Data curation (supporting); Project administration (lead); Writing – review & editing (lead).

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material Appendix S1 of this article.

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SUPPORTING INFORMATION

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