Risk Factors Associated With Mortality in Hypersensitivity Pneumonitis: A Meta-analysis

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Abstract

Purpose: Hypersensitivity pneumonitis (HP), an immune-mediated form of diffuse parenchymal lung disease (DPLD), is triggered by inhalation of a wide variety of allergens in susceptible individuals. Several studies suggest that the death rate associated with this disease has increased significantly in recent years. This meta-analysis investigates the significant clinico-radiological characteristics which may be appraised as potential risk factors associated with disease mortality.

Methods: Extensive literature search was conducted for original articles published between January 2009 and April 2021 through PubMed, Google Scholar, EMBASE, and Cochrane Library using the keywords: “hypersensitivity pneumonitis”, “hazard ratio” and “mortality”.

Results: A total of 21 independent studies related to mortality of HP subjects could be identified. The combined results of univariate and multivariate analysis suggest that older age [univariate odds ratio (OR) 1.038 (1.028-1.048); multivariate OR 1.036, (1.025-1.046)], male subjects [univariate OR 1.508, (1.240- 1.834); multivariate OR 1.396, (1.004-1.943)], honeycombing [univariate OR 1.086 (1.065- 1.108); multivariate OR 1.121 (1.070- 1.175)] and traction bronchiectasis [univariate OR 1.141 (1.092- 1.192); multivariate OR 1.107 (1.048-1.169)] are significantly associated with mortality risk of HP subjects. Further, forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLco), ground glass opacity (GGO) and mosaic attenuation were associated with lower risk of all-cause mortality. Although smoking status correlated with mortality risk in these patients, the findings appeared to be insignificant.

Conclusion: Individual male subjects with older age and presence of extensive fibrosis, i.e., honeycombing and traction bronchiectasis experience an increased mortality risk.

Introduction

Hypersensitivity pneumonitis (HP), an immune-mediated form of diffuse parenchymal lung disease (DPLD), is triggered by inhalation of a wide variety of allergens in susceptible individuals [1]. The prevalence of HP differs significantly among and even within countries, due to factors such as antigens distribution, geographical location, culture, and climate [2]. An European and a Danish study report that HP accounts for 4–13% and 7% of all DPLD cases, respectively [3, 4]. HP comprises of 47.8% of the total number of DPLD cases among Indian population [5].

Several studies suggest that the rate of death associated with this granulomatous disease has increased significantly in recent years [6]. An earlier United States (US) population-based mortality study reported a significant increase in death rate from 0.09 to 0.29 per million between 1980 and 2002 [7]. A recent study, again on the US population, reports that HP-related mortality rate increased considerably from 0.12 per million to 0.68 per million between 1988 and 2016 [8]. Most of the mortality associated data are from patients of Western countries; data from Asian patient population remains scarce. Only a limited number of reports exist on mortality assessment of HP in Asian population, with Japan and China reporting a median survival time of 74.5 months for chronic HP and 83 months for HP, respectively [9, 10]. Despite the

high incidence rate, not all patients diagnosed with HP die or need a lung transplant. It is likely that some key factors increase the risk of death or cause critical medical complications in these patients. Identification of such modifiable risk factors associated with mortality in HP patients is, therefore, well-realized.

In addition to radiological factors, population-based studies suggest involvement of other clinical factors that have a direct influence on mortality of HP patients [11]. Meta-analysis of risk factors for other DPLD subtypes, such as idiopathic pulmonary fibrosis (IPF) and sarcoidosis are documented [12]. However, possibly due to inconsistencies and paucity of evidence, meta-analysis of global risk factors in HP is yet to be reported. Herein, we provide a systematic review and meta-analysis to sharp focus on the significant clinico-radiological characteristics which may be appraised as potential risk factors associated with mortality in HP patients.

Methods

Literature search

Extensive literature search was conducted by two independent investigators (SDG and AB) for original articles published between 1st January 2009 and 30th April 2021. Both authors searched through PubMed, Google Scholar, EMBASE, and Cochrane Library using the keywords: “hypersensitivity pneumonitis”, “hazard ratio” and “mortality”. In addition, references of relevant research papers were manually screened for additional eligible articles. Finally, inconsistencies associated with the extracted data were discussed with the third and fourth author/reviewer and suitably addressed. The search flow diagram of this meta-analysis is demonstrated in Fig. 1.

Study selection

The present review includes literature fulfilling the following criteria: (a) full-text access of articles (b) information presented in English (c) peer-reviewed accepted/published articles (d) literature published on and after 1st January 2009 (e) multiple factors available for the survival of HP. Exclusion criteria were as follows: (a) case reports (b) letters to the editor (c) clinical commentaries (d) narrative reviews and (v) case series.

Data extraction

Two reviewers extracted information from all original articles selected for this meta-analysis. The extracted information included: (1) authors’ names (2) publication year (3) sample size (4) country and (5) the diagnostic criteria for HP. The present manuscript is prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Statistical analysis

The strength of association between predefined outcomes and potential factors was determined using odds ratios (OR). Ten factors including 3 demographics (age, sex, smoking status), forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLco) and 5 radiological [ground glass opacity (GGO), mosaic attenuation, reticulation, honeycombing and traction bronchiectasis] parameters were considered to be the probable risk factors for the mortality of HP patients and heterogeneity calculated for each parameter. The effect size was considered to be the overall OR and reported with a 95% confidence interval. Heterogeneity was assessed for univariate and multivariate data by Cochrane's Q statistics. The I^2 value in the forest plot, calculated using STATA software 15.0 (StataCorp, TX, USA), reflects statistical heterogeneity between studies included in the meta-analysis. It determines the significance of the heterogeneity test and is sub-divided into four categories, i.e., 1. not important (0%–30%), 2. moderate important (30%–50%), 3. substantial important (50%–70%) and 4. considerable important (70%–100%). A funnel plot was generated to demonstrate publication bias of the covariates (log OR vs standard error of log OR).

Results

Overview of the included studies

Data of 3077 HP patients from 21 independent studies [10,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33] are extracted and included in the present meta-analysis. For an isolated study, the highest sample size was found to be 753 [28] while the lowest number corresponded to 23 cases of HP [31]. The characteristics of the studies included are summarized in Table 1. Majority of these studies were conducted in US (8/21), followed by United Kingdom (UK) (4/21) and Japan (3/21). The remaining six studies were conducted in South Korea, Brazil, Germany, Spain, Denmark and China.

Statistical analysis

Based on all studies included, a total of 10 potential risk factors for all-cause mortality in HP patients could be identified. The effects of these potential risk factors, including age, sex, smoking status, FVC, DL_{CO}, honeycombing, mosaic attenuation, reticulation, GGO and traction bronchiectasis are explored using univariate analysis. We found only 1 study reporting multivariate hazard ratio for reticulation [18]; hence this factor was excluded and the other 9 potential risk factors considered for multivariate analysis.

Univariate analysis

Univariate analysis identified a total of 6 potential risk factors which were statistically significant for pooled data in meta-analysis. These potential risk factors included older age [overall OR 1.038 (1.028-1.048); I^2: 40.8%, p value 0.077], male subjects [overall OR 1.508 (1.240- 1.834); I^2: 32.4%, p value 0.180], honeycombing [overall OR 1.086 (1.065- 1.108); I^2: 86.5%, p value <0.0001], mosaic attenuation [overall OR 1.016 (1.000-1.032); I^2: 72.3%, p value 0.001], reticulation [overall OR 1.021 (1.014-1.029); I^2: 95.0%, p

value <0.0001], and traction bronchiectasis [overall OR 1.141 (1.092- 1.192); I^2: 88.4%, p value <0.0001]. Further FVC, DLco and GGO were associated with lower risk of all-cause mortality (Fig. 2 and 3). Although smoking status could be correlated with mortality risk in these patients, the findings were not significant (Table S1).

Multivariate analysis and identification of risk factors

Multivariate analysis indicated significant association between 4 cofactors and mortality of HP subjects. These potential risk factors emerged to be age [overall OR 1.036 (1.025-1.046); I^2: 58.0%; p value 0.011], sex (male) [overall OR 1.396 (1.004-1.943); I^2: 0.0%; p value 0.779], honeycombing [overall OR 1.121 (1.070-1.175); I^2: 89.4%; p value <0.0001] and traction bronchiectasis [overall OR 1.107 (1.048-1.169); I^2: 83.3%; p value 0.003] (Fig. 4 and 5). Multivariate analysis revealed mosaic pattern is not associated with mortality risk. The association of smoking status, FVC, DLco and GGO with disease mortality shows similar trend as univariate result (Table S2).

The combined results of univariate and multivariate analysis suggest that patients with advanced age, male subjects and radiological features including honeycombing and traction bronchiectasis are significantly associated with the mortality risk. However, heterogeneity was high regarding most of the outcomes. The funnel plots that were produced to assess publication bias are shown in Fig. S1.

Discussion

The mortality rate of HP has increased rapidly in the last few decades. Assessment of association between various risk factors and mortality of patients with HP has attracted considerable attention of clinicians from various countries. This is the first attempt to ascertain clinical mortality predictors of HP by meta-analysis. In this systematic review and meta-analysis, we identified 21 studies describing potential risk factors that could be accountable for the mortality of patients with HP.

We observed a higher mortality risk in elderly participants. This is not surprising since advanced age is a well-known risk factor associated with poor prognosis in various DPLD subtypes. Moreover, various co-morbidities develop at this stage [34, 35]. Also, a growing body of evidence suggests that male HP patients have poor chances of survival [36], which is in agreement with our observations. Clarson and co-workers have shown that male DPLD patients are at a higher risk of developing ischemic heart disease and myocardial infarction, which might influence survival of these subjects [37].

Tobacco smoke is reported to cause damage to the alveolar epithelium and leads to poor prognosis [38]. Interestingly, we observed no significant association between smoking status and disease mortality. Our findings are in accordance with previous studies [39, 40]. The presence of GGO, mosaic attenuation, lower FVC and DLco did not appear to increase mortality risk in HP subjects. Earlier studies also demonstrate a similar trend, thereby supporting our findings [29].

The presence of honeycombing and traction bronchiectasis pattern emerges to be the radiological predictor of mortality for patients with HP. Walsh et al., over nearly a 7-year period, studied the individual high-resolution computed tomography (HRCT) patterns and physiologic indices of patients reporting to a UK-based hospital and diagnosed with chronic HP. The authors found the presence of extensive traction bronchiectasis and honeycombing to strongly associate with disease mortality in chronic HP patients [32]. In another study, Mooney et al. have shown that a greater extent of honeycombing, reticular and traction bronchiectasis is associated with shortened life span in patients with HP [25]. This is in agreement with the findings of Jacob et al., where honeycombing, reticulation and traction bronchiectasis are suggested to be strong predictors of mortality in HP patients [20, 21]. In a recent study, Salisbury et al. have compared the survival time and pulmonary function changes of patients with HP and IPF by radiologic phenotype. HP patients with non-honeycomb fibrosis could be associated with longer survival period than IPF cases. Furthermore, HP and IPF subjects with honeycombing exhibited poor survival and significant decline in predicted FVC% [29]. In another very interesting study conducted over a 15-year period at the Tokyo Medical and Dental University Hospital, Tateishi et al. defined the HRCT features of acute, recurrent, and insidious cases of 112 bird fancier's lung at the time of initial diagnosis and assessed the HRCT changes over the follow-up period. The authors observed that GGO and centrilobular nodules were predominantly present in acute and recurrent HP, whereas honeycombing was the most prominent feature in insidious and chronic HP. The authors also suggest that patients with the presence of radiographic honeycombing pattern with airspace consolidation are associated with a decreased survival rate [30].

In another population-based single-centric study in China, Wang et al. explored the incidence, clinical characteristics and outcome of 101 patients with HP. Interestingly, in contrast to our analysis, the group found unidentified exposure and low baseline total lung capacity predicted percentage to be the independent risk factors as survival predictors in all subjects. Fibrosis on chest HRCT as a clinical variable was not observed to be statistically significant [10]. Two additional studies are reported where the findings are contrary to our analysis. First, Hanak et al. have investigated the association between survival clinical features including HRCT patterns and spirometric values of 69 patients with subacute or chronic HP. It is suggested that the presence of fibrosis on HRCT images and pulmonary function impairment is associated with reduced survival and an indicator of disease prognosis. However, honeycombing independently could not be significantly correlated with mortality [41]. Second, Sahin and colleagues have retrospectively compared HRCT features of HP patients suggestive of fibrosis with histologic fibrosis score. They concluded that though HRCT findings consisting of extensive reticular pattern, traction bronchiectasis and honeycombing seem to be closely related to the presence of fibrosis in chronic HP; it is the presence of histologic fibrosis and not the CT characteristics which significantly relate to decreased survival [42].

The present study has several limitations that should be acknowledged. First, all studies included are retrospective in nature. Second, subgroup analyses could not be performed due to limited sample size for all the studies. Third, individual observations are clinically different in terms of age, sex, ethnicity, disease severity and diagnostic procedures, which may have contributed to significant heterogeneity in the

present analysis. Nonetheless, well-defined data extraction, literature search, and quality assessment does strengthen our observations.

Conclusion

A number of clinical traits such as age, sex, smoking status, DLco, FVC, radiological features including GGO, mosaic attenuation, reticulation, honeycombing and traction bronchiectasis of patients with HP are analyzed to identify the major risk factors contributing to disease mortality. Age, male subjects, honeycombing and traction bronchiectasis emerged to be the significant risk factors. Multicentric observational and interventional studies are suggested to validate these findings. Also, it is desirable to explore the association of the identified risk factors with disease progression.

Abbreviations

DLco: Diffusing capacity for carbon monoxide

DPLD: Diffuse parenchymal lung disease

FVC: Forced vital capacity

GGO: Ground glass opacity

HP: Hypersensitivity pneumonitis

HRCT: High-resolution computed tomography

IPF: Idiopathic pulmonary fibrosis

OR: Odds ratio

US: United states

Declarations

Funding

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Conflicts of interest

None

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

S. D. had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the data. S.D. and A.B. conducted the literature search, extracted the results, performed the meta-analyses; and drafted the manuscript. S.R.C and K.C revised the manuscript.

Ethics approval

No ethical approval was necessary for the present study.

Consent to participate

Not applicable

Consent for publication

Not applicable

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Tables

Table 1 Characteristics of the included studies in meta-analysis

Sl no.	Study	Year	Country	Number of patients with HP (n)	Age (years)	Gender (% men)	Diagnosis
1	Adegunsoye et al.[14]	2016	United States	120	63 ±10	41.6	• HRCT features compatible with HP • Surgical lung biopsy • Exclusion of other alternative diseases • Presence of antibodies to serum precipitins
2	Adegunsoye et al.[15]	2019	United States	143	-	-	• Multidisciplinary discussion
3	Choe et al. [16]	2020	South Korea	91	59.1 ± 10.7	38.5	• Surgical or transbronchial lung biopsy • Multidisciplinary discussion
4	Chung et al. [17]	2017	United States	110	61±10	48.18	• Multidisciplinary discussion • Surgical lung biopsy
5	Chung et al. [18]	2017	United States	132	62.1±11.5	39.39	• Multidisciplinary approach
6	Fernández Pérez et al. [19]	2013	United States	142	58±12	52.81	• Presence of compatible clinical features • Abnormal pulmonary function tests • Exclusion of other diseases • Presence of precipitating antibodies

							(supportive but not required) • Surgical lung biopsy
7	Jacob et al. [20]	2017	United Kingdom	116	58·5#	33.62	• Multi-disciplinary discussion
8	Jacob et al. [21]	2017	United Kingdom	98	59#	38.77	• Multi-disciplinary discussion
9	Jacob et al. [22]	2018	United Kingdom	233	62#	39.91	• Multi-disciplinary discussion
10	Lima et al. [23]	2009	Brazil	103	56±13	37.86	• Relevant exposure preceding respiratory symptoms • Presence of episodic/ persistent respiratory symptoms • HRCT feature • Consistent histopathological findings • No other identifiable cause for the lung disease Precipitin tests and bronchoscopy were not performed in the majority of cases
11	Long et al. [24]	2016	Germany	72	57±2	38.88	• Clinical/ HRCT features • BALF characteristics and/or histopathological findings on biopsy
12	Mooney et al.[25]	2013	United States	177	60.76±11.3	30.50	• Consistent clinical history

							and features suggesting chronic respiratory symptoms • Abnormal pulmonary function tests • Compatible HRCT features • Exclusion of other disease that mimics HP • Biopsy confirmation when a plausible antigen exposure could not be identified
13	Nukui et al. [26]	2019	Japan	63	62.0±11.4	55.55	• Clinical, radiological, and histological criteria
14	Ojanguren et al.[27]	2018	Spain	160	60.9±12.9	41.87	• Blood tests (Specific IgG tests for birds and fungi) • Chest radiography • HRCT features • Spirometry • Static lung volumes, and DLco • BALF lymphocytosis and/or transbronchial biopsy or cryo-biopsy • Specific inhalation challenge in some case
15	Rittig et al. [28]	2019	Denmark	753	-	56.70	-
16	Salisbury et al.[29]	2019	United States	117	58.3±11.0	32.47	Presence of at least 2 criteria:

							• Surgical lung biopsy • Bronchoscopy with BAL lymphocytosis >20% • Plausible exposure history
17	Tateishi et al.[30]	2011	Japan	112	-	-	Acute bird-related HP • History of exposure to avian antigen • Consistent signs and symptoms of dyspnea, cough, and fever • Pathologic evidences • Antibodies and lymphocyte proliferative reactions against bird-related antigen • Positive provocation test Chronic bird-related HP • History of exposure of avian antigen • Avian antibodies and/or lymphocyte proliferative reactions against bird-related antigen • Evidence of pulmonary fibrosis with or without granulomas on histopathologic analysis or honeycombing on CT scans; • Progressive deterioration of pulmonary function

							(duration of one year) • HP related symptoms (duration of more than 6 months)
18	Tsutsui et al.[31]	2015	Japan	23	67.26±7.3	56.52	• Inhalation and environmental provocation test • Immunological examinations • Exposure of avian antigens
19	Walsh et al. [32]	2012	United Kingdom	92	55.1±12.6	43.47	• Multi-disciplinary discussion
20	Wang et al. [33]	2017	United States	119	60	36.97	• Pathologic or HRCT finding suggesting fibrosis presence • Respiratory symptom or HRCT evidence of DPLD for 4 months or longer duration when no histopathological evidence of fibrosis presence
21	Wang et al. [10]	2019	China	101	53.6±12.4	45.54	The major criteria include the following items • History of symptoms compatible with HP • Evidence of exposure to the offending antigen in the patient history or through detection by serum or bronchoalveolar lavage (BAL) fluid antibodies • HRCT features

- BAL lymphocytosis (if bronchoscopy was performed)
- histologic changes consistent with HP (if lung biopsy
- Positive natural challenge

The minor criteria are as follows:

- Bibasilar sacs
- Reduced DLco

and

- Arterial hypoxemia, either at rest or with exercise.

The diagnosis was confirmed if 4 of the major criteria and at least 2 of the minor criteria were fulfilled by the subjects

Age data are represented as mean ± SD unless otherwise stated; # Median value; HP: Hypersensitivity pneumonitis, DPLD: Diffuse parenchymal lung disease, HRCT: High-resolution computed tomography, BALF: Bronchoalveolar lavage fluid, FVC: Forced vital capacity, DLco: Diffusing capacity for carbon monoxide

Figures

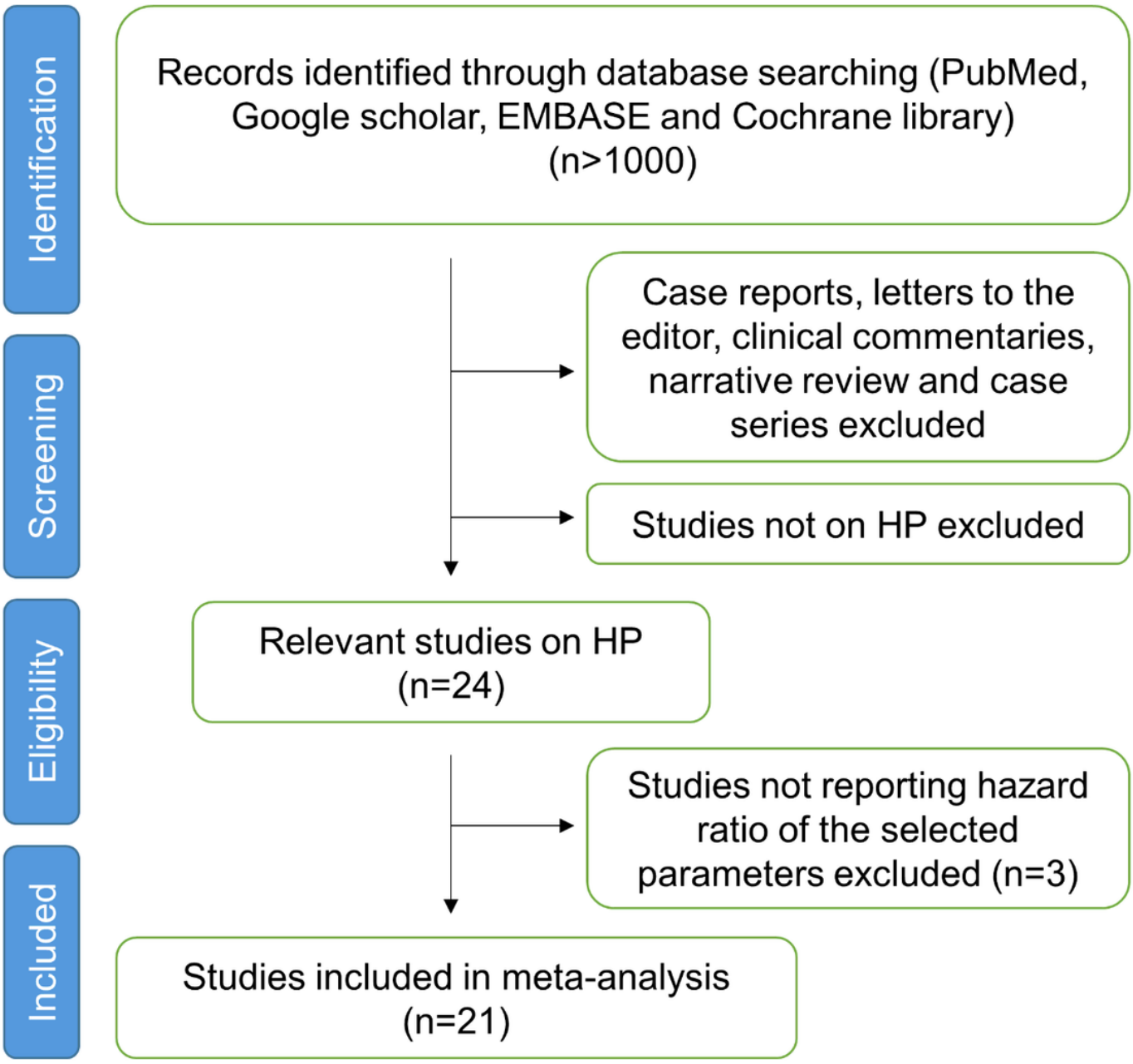

Figure 1

Flow diagram of search strategy for selection of articles included in meta-analysis

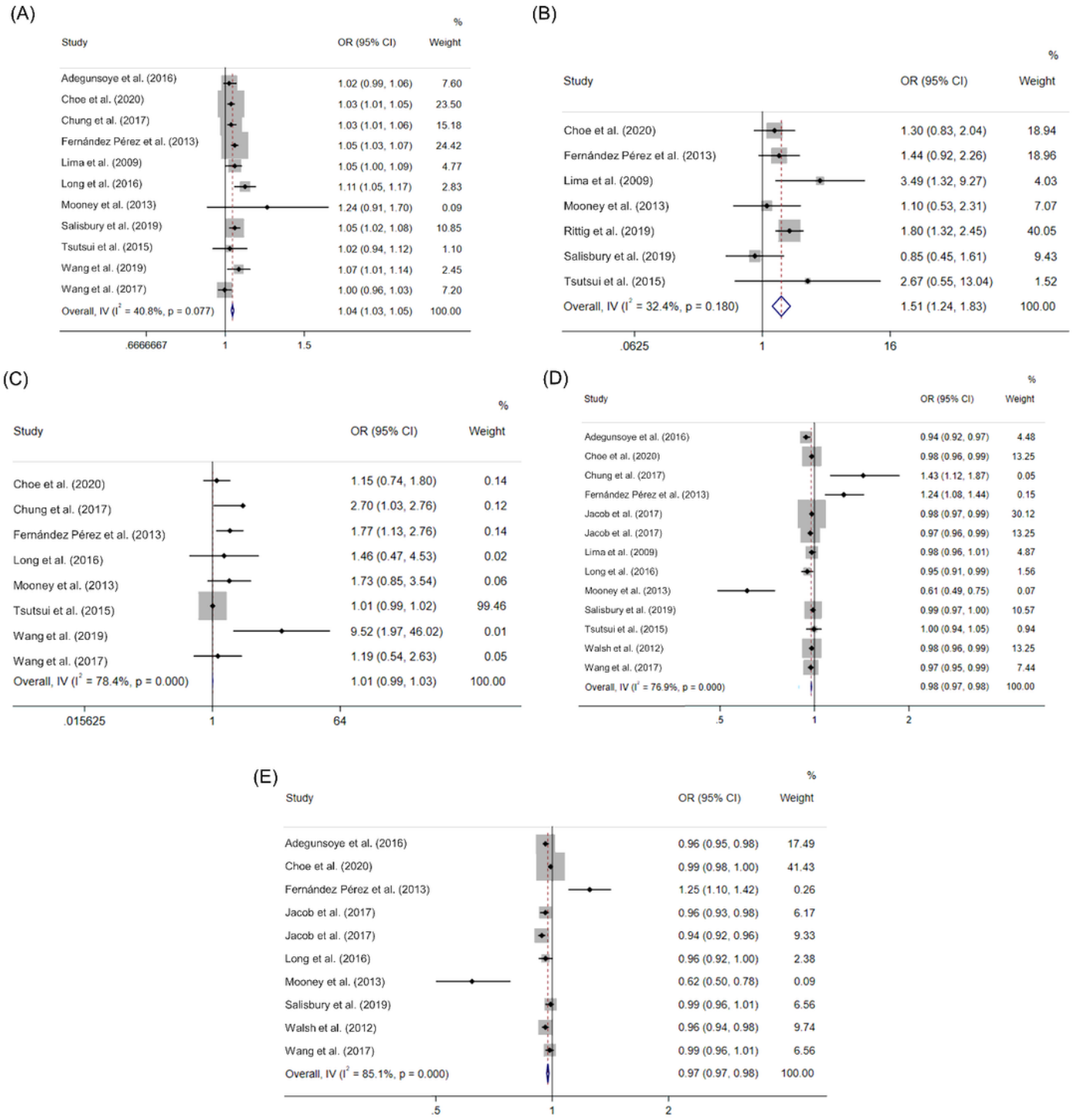

Figure 2

Forest plot of univariate data associating mortality risk with (A) age (B) sex (C) smoking history (D) forced vital capacity (FVC) and (E) diffusing capacity for carbon monoxide (DLco) in patients with hypersensitivity pneumonitis (HP)

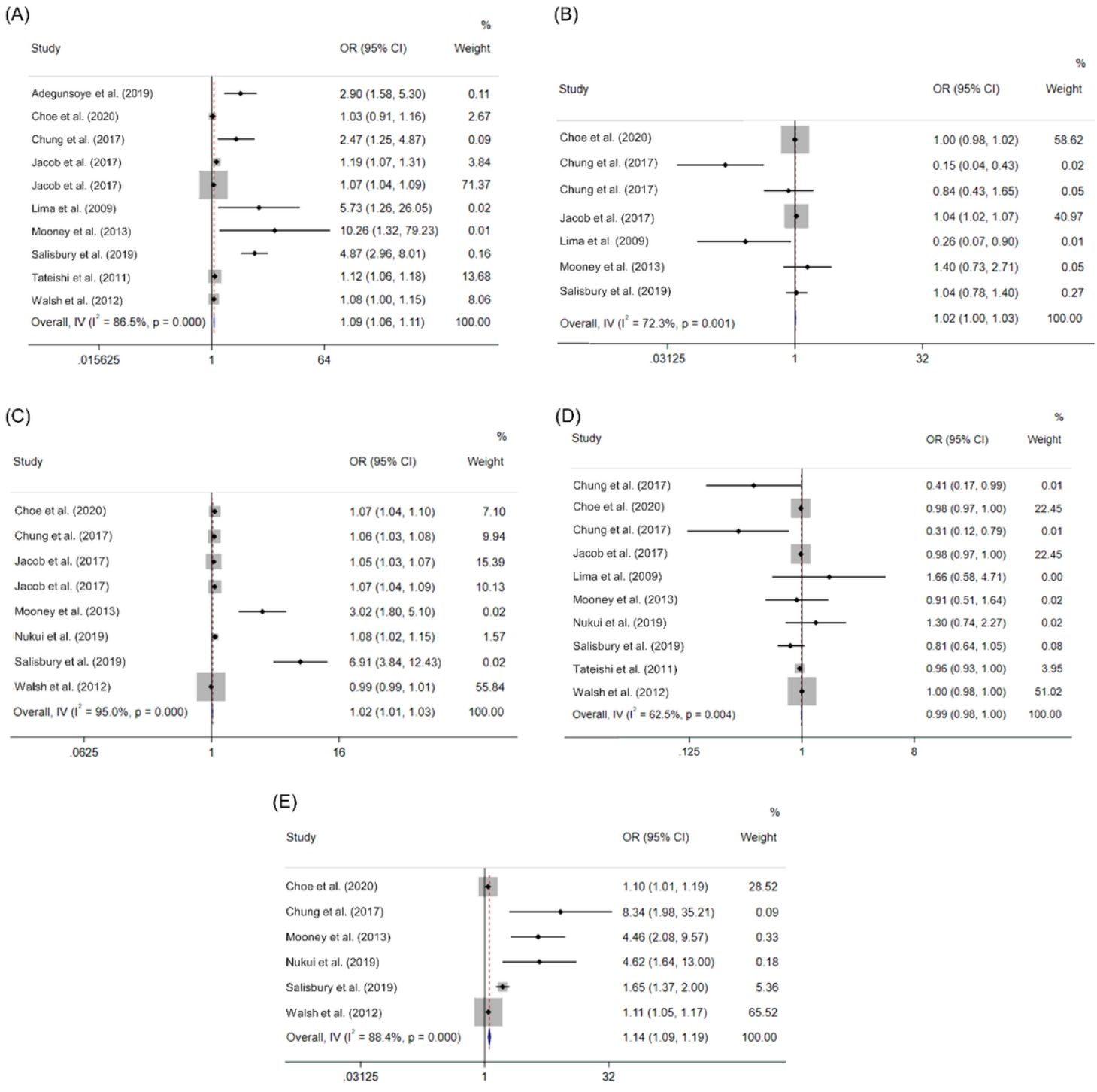

Figure 3

Forest plot of univariate data associating mortality risk with (A) honeycombing (B) mosaic attenuation (C) reticulation (D) ground glass opacity (GGO) and (E) traction bronchiectasis in patients with hypersensitivity pneumonitis (HP)

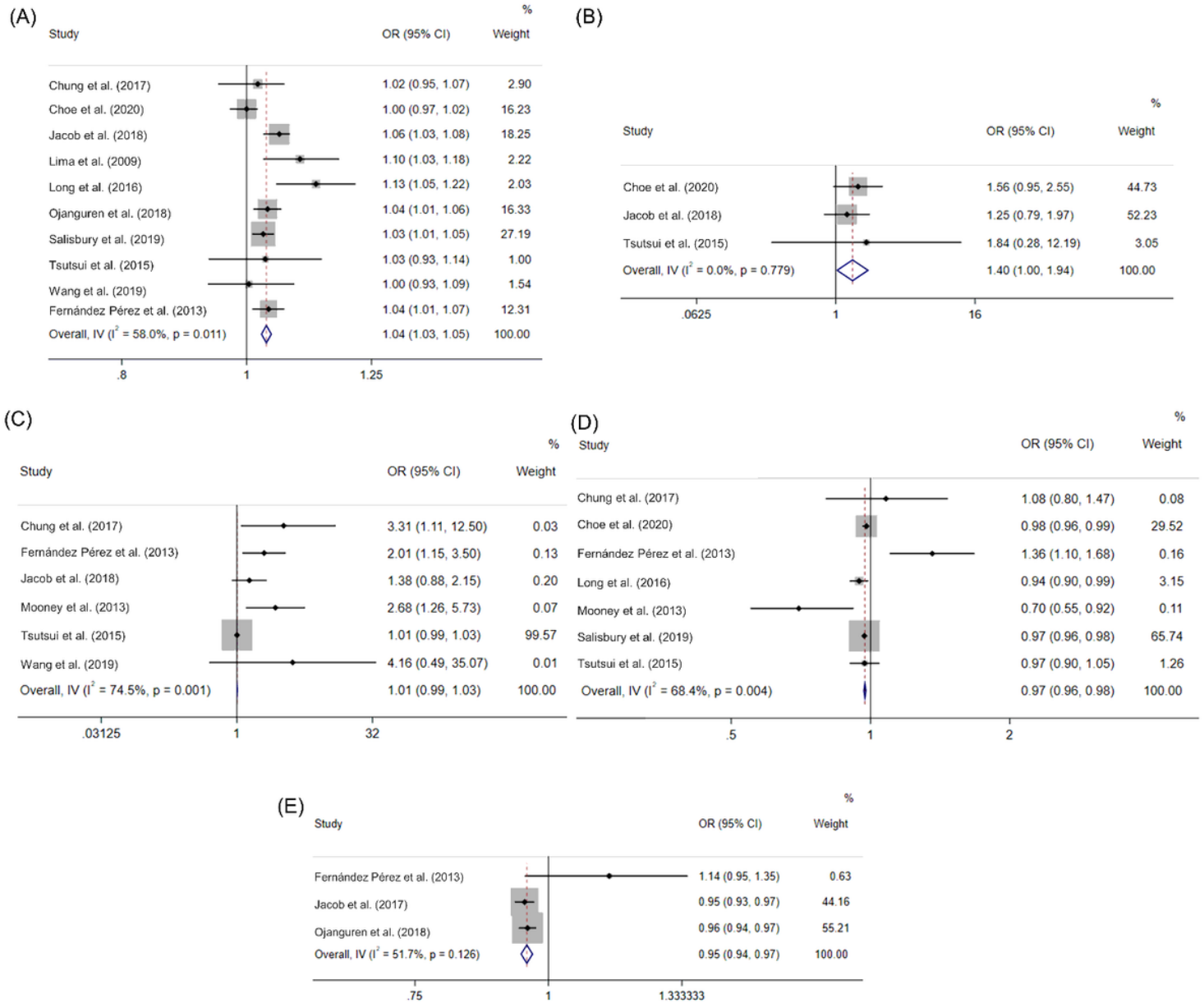

Figure 4

Forest plot of multivariate data associating mortality risk with (A) age (B) sex (C) smoking history (D) forced vital capacity (FVC) and (E) diffusing capacity for carbon monoxide (DLco) in patients with hypersensitivity pneumonitis (HP)

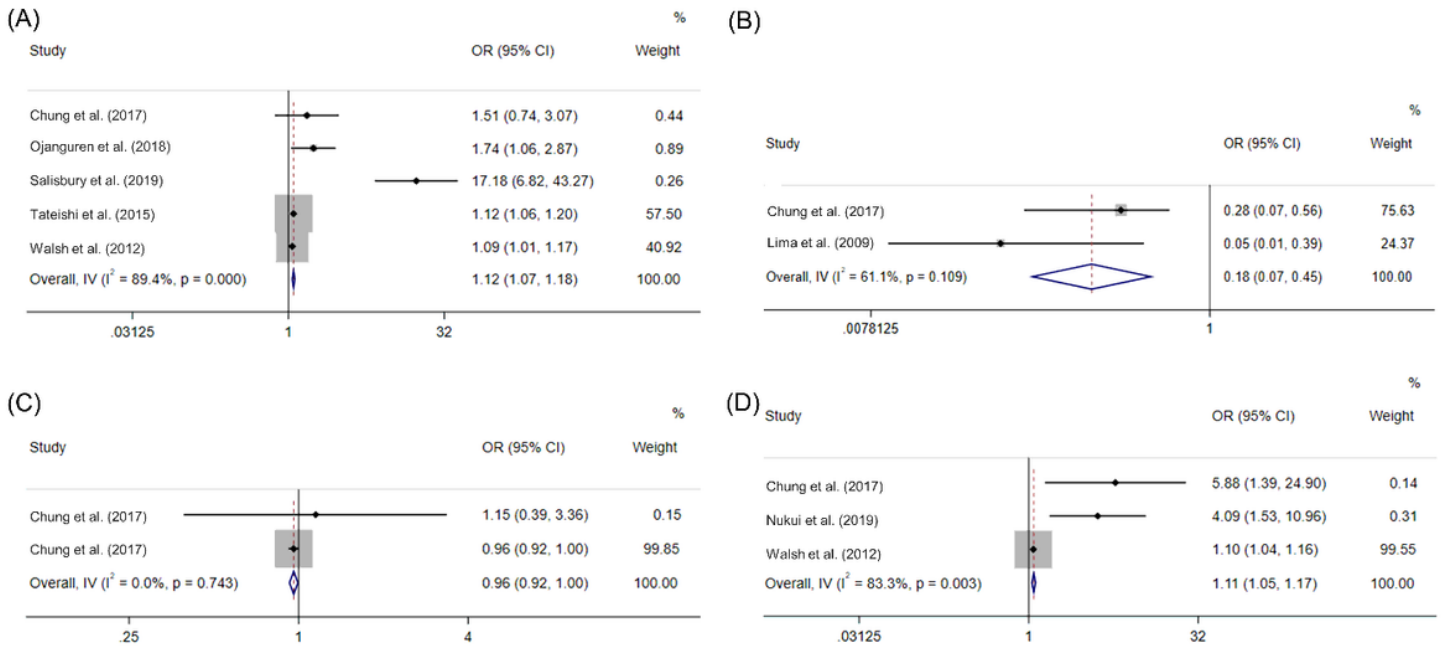

Figure 5

Forest plot of multivariate data associating mortality risk with (A) honeycombing (B) mosaic attenuation (C) ground glass opacity (GGO) and (D) traction bronchiectasis in patients with hypersensitivity pneumonitis (HP)

Supplementary Files

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- Supplementary.docx