Risk factors associated with mortality in hypersensitivity pneumonitis: a meta-analysis

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ABSTRACT
Background: Hypersensitivity pneumonitis (HP) related deaths have increased substantially in recent years. It is important to identify the risk factors of HP significantly associated with mortality to ensure close patient monitoring and assess disease progression.
Research design and methods: Extensive literature search was conducted in accordance with the PRISMA checklist. Literature search of PubMed, Embase, and Cochrane Library database between January 2009 and April 2021 using the terms 'hypersensitivity pneumonitis', 'hazard ratio', and 'mortality' identified 325 articles. A total of 22 independent original studies focusing on mortality of HP patients were assessed.
Results: This systematic review and meta-analysis suggests that increased age, male sex, honeycomb- and traction bronchiectasis patterns on high-resolution computed tomography (HRCT) images are the major mortality-related risk factors of patients with HP. In case of chronic HP, antigen exposure appeared to be an additional risk factor.
Conclusions: The clinico-radiological risk factors of mortality identified for HP will enable effective and close monitoring of patients, prognostication, and guide toward appropriate management decisions. However, association between the type of antigen and mortality remains to be explored.

1. Introduction

Hypersensitivity pneumonitis (HP), an immune-mediated 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 antigen diversity, 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 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 subjects of Western countries; data from Asian population remain 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 a high incidence rate, not all subjects 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 subjects. Identification of such modifiable risk factors associated with mortality of 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 the mortality of HP patients [11]. Meta-analysis of risk factors for idiopathic pulmonary fibrosis (IPF), another DPLD subtype, is well documented [12]. However, possibly due to inconsistencies and paucity of evidence, meta-analysis of global risk factors of 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 patients with HP.

2. Patients and methods

2.1. Literature search
Extensive literature search was conducted by two independent investigators (SDG and AB) for original articles published between 1 January 2009 and 30 April 2021. Both the authors searched through PubMed, Embase, and Cochrane Library database using the term 'hypersensitivity pneumonitis', 'hazard ratio', and 'mortality' and found a total of 325 results.
In addition, references of relevant research papers were manually screened for other 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 Figure 1.

2.2. 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 1 January 2009 (e) multiple factors associated with 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.

2.3. 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].

2.4. Statistical analysis

The strength of association between predefined outcomes and potential factors was determined using odds ratio (OR). The pooled OR and 95% confidence interval (CI) were determined using the random-effect model [14]. Twelve factors including age, sex, smoking status, forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLco), antigen exposure, prednisolone therapy, and radiological features including ground glass opacity (GGO), mosaic attenuation, reticulation, honeycombing, and traction bronchiectasis patterns 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% CI. Heterogeneity was assessed for univariate and multivariate data by Cochran’s Q statistics [15]. The I² 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: moderately important (30–50%), 3: substantially important (50–70%) and 4: considerably important (70–100%).

We also conducted publication bias and sensitivity analysis using metafor R package for Windows 3.4.0. Studentized residuals and Cook’s distances are used to evaluate outliers and/or identify influential studies in context of the model [16].

![Figure 1. Flow diagram of search strategy used for selection of articles included in the meta-analysis.](image)

HR: hazard ratio; HP: hypersensitivity pneumonitis.
Studies with a studentized residual larger than the 
\[
\left[ \frac{0.05}{12 \times k} \right] ^{1/2}
\]
percentile of a standard normal distribution are considered to be potential outliers (i.e., using a Bonferroni correction with two-sided α = 0.05 for k studies included in the meta-analysis). Studies with a Cook’s distance larger than the median plus six times the interquartile range of the Cook’s distance are considered to be influential.

Potential publication bias was further detected by Egger’s test, which was applied to measure the significance of asymmetry among the studies included [17]. A funnel plot was further generated to demonstrate publication bias of the covariates. Plots including (1) externally standardized residuals, (2) difference in fits (DFITS) values, (3) Cook’s distances, (4) covariance ratios, (5) leave-one-out estimates of the amount of heterogeneity, (6) leave-one-out values of the test statistics for heterogeneity, (7) hat values, and (8) weights identified the studies that had a strong influence on the results. Furthermore, we conducted sensitivity analyses to identify the studies at lower risk of bias.

3. Results

3.1. Overview of the included studies

Data of 3152 HP subjects from 22 independent studies [10,18–38] were extracted and included in the present meta-analysis. For an isolated study, the highest sample size was found to be 753 [32], while the lowest number corresponded to 23 cases [35]. The characteristics of the studies included are summarized in Table 1. Most of these studies have been conducted in the US (8/22), followed by United Kingdom (UK) (4/22) and Japan (4/22). The remaining six studies were conducted in South Korea (n = 1), Brazil (n = 1), Germany (n = 1), Spain (n = 1), Denmark (n = 1), and China (n = 1).

3.2. Statistical analysis

Based on all studies included, a total of 12 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, DLCO, antigen exposure, prednisolone therapy, GGO, mosaic attenuation, reticulation, honeycombing, and traction bronchiectasis are explored using univariate analysis. We found only one study reporting multivariate hazard ratio for reticulation [22] and prednisolone therapy [29]; hence, these two factors were excluded and the other 10 potential risk factors considered for multivariate analysis.

3.3. Univariate analysis

Univariate analysis identified a total of 7 potential risk factors which were statistically significant for the pooled data. These potential risk factors included older age [overall OR 1.038 (1.028–1.048); \( \hat{i}^2: 40.8\% \), \( p = 0.077 \)], male subjects [overall OR 1.508 (1.240–1.834); \( \hat{i}^2: 32.4\% \), \( p = 0.180 \)], antigen exposure [overall OR 1.470 (1.073–2.016); \( \hat{i}^2: 74.4\% \), \( p = 0.002 \)], mosaic attenuation [overall OR 1.016 (1.000–1.032); \( \hat{i}^2: 72.3\% \), \( p = 0.001 \)], reticulation [overall OR 1.021 (1.014–1.029); \( \hat{i}^2: 95.0\% \), \( p < 0.0001 \)], honeycombing [overall OR 1.086 (1.065–1.108); \( \hat{i}^2: 86.5\% \), \( p < 0.0001 \)], and traction bronchiectasis pattern [overall OR 1.141 (1.092–1.192); \( \hat{i}^2: 88.4\% \), \( p < 0.0001 \)]. Although smoking status and prednisolone therapy could be correlated with mortality risk in these subjects, the findings were not significant (Table 2).

3.4. Multivariate analysis and identification of risk factors

Multivariate analysis indicated significant association between four cofactors and mortality of patients with HP. These potential risk factors emerged to be older age [overall OR 1.036 (1.025–1.046); \( \hat{i}^2: 58.0\% \), \( p = 0.011 \)], sex (male) [overall OR 1.396 (1.004–1.943); \( \hat{i}^2: 0.0\% \), \( p = 0.779 \)], honeycombing [overall OR 1.121 (1.070–1.175); \( \hat{i}^2: 89.4\% \), \( p < 0.0001 \)] and traction bronchiectasis [overall OR 1.107 (1.048–1.169); \( \hat{i}^2: 83.3\% \), \( p = 0.003 \)]. Multivariate analysis revealed that mosaic pattern is not associated with the risk of mortality; also, association of antigen exposure with the risk of mortality was found to be non-significant. The association of smoking status, FVC, DLco, and GGO with disease mortality indicated a trend similar to that of univariate analysis data (Table 3).

The combined results of univariate and multivariate analysis suggest that advanced age, male sex, and radiological features including honeycombing and traction bronchiectasis are significantly associated with high mortality risk of patients with HP (Figures 2 and 3). However, heterogeneity was high for most of the outcomes.

3.5. Publication bias

Funnel plots for assessing publication bias are shown in Figure 4. These plots revealed no visual asymmetry, hence suggesting the absence of publication bias for age, sex, and traction bronchiectasis. However, for honeycombing and traction bronchiectasis, the regression test indicated asymmetry in funnel plot (\( p < 0.0001 \)). No such asymmetry was observed for the rank correlation test (\( p = 0.1557 \) for honeycombing and \( p = 0.4694 \) for traction bronchiectasis). Interestingly, for age and sex, neither the rank correlation nor the regression test indicated any funnel plot asymmetry (\( p = 0.5423 \) and \( p = 0.1713 \), respectively, for age; \( p = 1.0000 \) and \( p = 0.5519 \), respectively, for sex (male)). This was supported by non-significant values of Egger’s regression test for age (\( p = 0.3668 \)) and male sex (\( p = 0.9693 \)), and significant values for honeycombing (\( p = 0.0039 \)) and traction bronchiectasis (\( p = 0.0059 \)) (weighted regression with multiplicative dispersion).

An examination of the significant parameters indicated no outliers in case of age and sex. According to Cook’s distances, none of the studies could be considered as to be overly influential for age and sex risk models. However, one study appeared to be a potential outlier in context of the risk models for honeycombing and traction bronchiectasis patterns (Figure S1–S4) [33]. Sensitivity analyses on the influence of outliers indicated substantial statistical heterogeneity. Potential outliers were screened by
| SI no. | References          | Type of study      | Year       | Country    | Number of subjects with HP (n) | Age (years) | Gender (% male) | Duration of follow-up | Outcome                  | Diagnosis |
|--------|---------------------|--------------------|------------|------------|-------------------------------|-------------|------------------|------------------------|--------------------------|-----------|
| 1.     | Wang et al. [10]    | Retrospective cohort study | 2019       | China      | 101                           | 53.6 ± 12.4 | 45.54            | January 2009 - December 2017 | All-cause mortality     | The major criteria include the following items:  
  - History of symptoms compatible with HP  
  - Evidence of exposure to the offending antigen according to clinical history or by detection of antibodies in serum or bronchoalveolar lavage (BAL) fluid  
  - HRCT features  
  - BAL lymphocytosis (if bronchoscopy performed)  
  - Histologic changes consistent with HP (if lung biopsy performed)  
  - Positive natural challenge  
  The minor criteria are as follows:  
  - Bibasilar sacs  
  - Reduced DLco  
  - Arterial hypoxemia, either at rest or with exercise  
  - Diagnosis confirmed if four of the major criteria and at least two of the minor criteria met |
| 2.     | Adegunsoye et al. [18] | Retrospective cohort study | 2016       | United States | 120                           | 63 ± 10     | 41.6             | 1 January 2006 - February 28, 2015 | All-cause mortality     | HRCT features compatible with HP  
  - Surgical lung biopsy  
  - Exclusion of other alternative diseases  
  - Presence of antibodies to serum precipitins |
| 3.     | Adegunsoye et al. [19] | Retrospective cohort study | 2019       | United States | 143                           | -           | -                | January 2006 - July 2016 | All-cause mortality     | Multidisciplinary discussion |
| 4.     | Choe et al. [20]    | Retrospective cohort study | 2020       | South Korea | 91                            | 59.1 ± 10.7 | 38.5             | January 2002 - December 2017 | Fibrotic progression-free survival | Surgical or transbronchial lung biopsy  
  - Multidisciplinary discussion |
| 5.     | Chung et al. [21]   | Retrospective cohort study | 2017       | United States | 110                           | 61 ± 10     | 48.18            | January 1982 - July 1, 2015 | All-cause mortality     | Multidisciplinary discussion  
  - Surgical lung biopsy |
| 6.     | Chung et al. [22]   | Retrospective cohort study | 2017       | United States | 132                           | 62.1 ± 11.5 | 39.39            | 2006-2015              | All-cause mortality     | Multidisciplinary approach |
| 7.     | Fernández Pérez et al. [23] | Retrospective cohort study | 2013       | United States | 142                           | 58 ± 12     | 52.81            | January 1982 - January 1, 2008 | All-cause mortality     | Presence of compatible clinical features  
  - Abnormal pulmonary function tests  
  - Exclusion of other diseases  
  - Presence of precipitating antibodies (supportive but not required)  
  - Surgical lung biopsy |
| 8.     | Jacob et al. [24]   | Retrospective cohort study | 2017       | United Kingdom | 116                           | 58 - 5³     | 33.62            | January 2007 - July 2011 | All-cause mortality     | Multidisciplinary discussion |
| 9.     | Jacob et al. [25]   | Retrospective cohort study | 2017       | United Kingdom | 98                            | 59³         | 38.77            | January 2000 - December 2006 | All-cause mortality     | Multidisciplinary discussion |
| 10.    | Jacob et al. [26]   | Retrospective cohort study | 2018       | United Kingdom | 233                           | 62³         | 39.91            | January 2007 - July 2014 | All-cause mortality     | Multidisciplinary discussion |
| 11.    | Lima et al. [27]    | Retrospective cohort study | 2009       | Brazil      | 103                           | 56 ± 13     | 37.86            | January 1995 - December 2006 | All-cause mortality     | Relevant exposure preceding respiratory symptoms  
  - Presence of episodic/persistent respiratory symptoms  
  - HRCT features  
  - Consistent histopathological findings  
  - No other identifiable cause of the lung disease  
  - Precipitin test and bronchoscopy not performed in most of the cases |

(Continued)
Table 1. (Continued).

| SI no. | References | Type of study | Year | Country | Number of subjects with HP (n) | Age (years) | Gender (% male) | Duration of follow-up | Outcome | Diagnosis |
|--------|------------|---------------|------|---------|-------------------------------|-------------|-----------------|----------------------|---------|-----------|
| 12.    | Long et al. [28] | Retrospective cohort study | 2016 | Germany | 72 | 57 ± 2 | 38.88 | January 2007 – December 2013 | All-cause mortality | • Clinical/HRCT features  
• BALF characteristics and/or histopathological findings on biopsy |
| 13.    | Mooney et al. [29] | Retrospective cohort study | 2013 | United States | 177 | 60.76 ± 11.3 | 30.50 | March 2000 – October 2010 | All-cause mortality | • Consistent clinical history and features suggesting chronic respiratory symptoms  
• Abnormal pulmonary function tests  
• Compatible HRCT features  
• Exclusion of other diseases that mimic HP  
• Biopsy confirmation when a plausible antigen exposure not identified |
| 14.    | Nukui et al. [30] | Retrospective cohort study | 2019 | Japan | 63 | 62.0 ± 11.4 | 55.55 | January 2004 – December 2013 | All-cause mortality | • Clinical, radiological, and histological criteria |
| 15.    | Ojanguren et al. [31] | Retrospective cohort study | 2018 | Spain | 160 | 60.9 ± 12.9 | 41.87 | 1 January 2004 – December 31, 2013 | All-cause mortality | • Blood tests (specific IgG tests for birds and fungi)  
• Chest radiography  
• HRCT features  
• Spirometry  
• Static lung volumes  
• DLco test  
• BALF lymphocytosis and/or transbronchial biopsy or cryo-biopsy  
• Specific inhalation challenge in some cases |
| 16.    | Rittig et al. [32] | Retrospective cohort study | 2019 | Denmark | 753 | - | 56.70 | 1998–2010 | All-cause mortality | • Not mentioned |
| 17.    | Salisbury et al. [33] | Retrospective cohort study | 2019 | United States | 117 | 58.3 ± 11.0 | 32.47 | 1 February 2009 – August 31, 2014 | All-cause mortality | Presence of at least 2 criteria:  
• Surgical lung biopsy  
• Bronchoscopy with BAL lymphocytosis >20%  
• Plausible exposure history  
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 to 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 1 year)  
• HP-related symptoms (duration of more than 6 months)  
• Inhalation and environmental provocation test  
• Immunological examination  
• Exposure of avian antigen  
• Multidisciplinary discussion |
| 18.    | Tateishi et al. [34] | Retrospective cohort study | 2011 | Japan | 112 | - | - | October 1992 – December 2007 | All-cause mortality | |
| 19.    | Tsutsui et al. [35] | Retrospective cohort study | 2015 | Japan | 23 | 67.26 ± 7.3 | 56.52 | July 2011 – June 2014 | All-cause mortality | |
| 20.    | Walsh et al. [36] | Retrospective cohort study | 2012 | United Kingdom | 92 | 55.1 ± 12.6 | 43.47 | January 2000 – December 2006 | All-cause mortality | |
visual inspection of their CI, followed by Baujat plots (Figure S5–S8).

### 3.6. Sub-group analysis

Sub-group analysis of the risk factors for chronic HP patients was performed. The findings are similar to our earlier observations for age [univariate overall OR: 1.03; multivariate overall OR: 1.02], antigen exposure [univariate overall OR: 1.81; multivariate overall

| Risk factors | Odds ratio (OR) | 95% Cl | P-value (OR) | Heterogeneity (I²) | P-value (I²) |
|--------------|----------------|--------|--------------|--------------------|--------------|
| Age          | 1.036          | 1.025–1.046 | 0.000      | 58.0%              | 0.011        |
| Sex (male)   | 1.396          | 1.004–1.943 | 0.047      | 0.0%               | 0.779        |
| Smoking status | 1.009         | 0.989–1.029 | 0.396      | 74.5%              | 0.001        |
| Antigen exposure | 1.512       | 0.916–2.496 | 0.106      | 78.6%              | 0.009        |
| FVC          | 0.972          | 0.964–0.981 | 0.000      | 68.4%              | 0.004        |
| DLco         | 0.954          | 0.941–0.968 | 0.000      | 51.7%              | 0.126        |
| GGO          | 0.960          | 0.921–1.001 | 0.056      | 0.0%               | 0.743        |
| Mosaic attenuation | 0.184     | 0.074–0.455 | 0.000      | 61.1%              | 0.109        |
| Honeycombing | 1.121          | 1.070–1.175 | 0.000      | 89.4%              | 0.000        |
| Traction bronchiectasis | 1.107 | 1.048–1.169 | 0.000      | 83.3%              | 0.003        |

FVC: forced vital capacity, DLco: diffusing capacity for carbon monoxide, GGO: ground glass opacity.
OR: 1.89, honeycombing [univariate overall OR: 1.11; multivariate overall OR: 1.10], and traction bronchiectasis patterns [univariate overall OR: 1.11; multivariate overall OR: 1.11]. The male sex risk factor was found to be statistically significant only for univariate analysis [univariate overall OR: 1.40; multivariate overall OR: 1.57]. The forest plots of significant risk factors in chronic HP patients are shown in Fig S9-S10. The rank correlation test shows no funnel.
plot asymmetry for univariate and multivariate analysis, indicating absence of publication bias (Figure S11-S12).

4. 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 clinico-radiological mortality predictors of HP by meta-analysis. In this systematic review and meta-analysis, we identified 22 studies describing potential risk factors that could be accountable for the mortality of patients with HP.

We observed a higher risk of mortality 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 [39,40]. Tobacco smoke is reported to cause damage to the alveolar epithelium and leads to poor prognosis [41]. Interestingly, we observed no significant association between smoking status and disease mortality. Our findings are in accordance with previously reported studies [42,43]. Further, the presence of GGO, mosaic attenuation, lower FVC, and DLco did not appear to increase the risk of mortality in patients with HP. Earlier studies also demonstrate a similar trend, thereby supporting our findings [33]. GGO is a common high-resolution computed tomography (HRCT) finding that can change to bronchiectasis or honeycombing over time [44]. Since it is a typical feature of early fibrosing alveoli, it is more likely to be diagnosed at an early stage [45]. Our overall analysis suggests that male patients have a higher

Figure 4. Funnel plots to assess publication bias.
risk factor for mortality. A growing body of evidence suggests that male patients with HP have poor chances of survival [46,47]. Carlson and coworkers observed that male patients with DPLD are at a higher risk of developing ischemic heart disease and myocardial infarction, which influence their survival [47]. It is reported that mortality rate for male patients with IPF is 7.36 per 100,000 as compared to 3.62 per 100,000 for females in the population of Finland [48]. In addition, similar to our univariate findings, other studies have also suggested that prolonged exposure to antigens or higher levels in the environment are associated with the progression of HP [49]. It is well accepted that removal of the triggering antigen results in considerable clinical improvement of the patient and may lead to disease resolution [23].

The presence of honeycombing and traction bronchiectasis pattern emerges to be the radiological predictor of mortality in patients with HP. Walsh et al., over nearly a 7-year period, studied the individual 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 cases [36]. In another study, Mooney et al. have shown that a greater extent of honeycombing, reticulation, and traction bronchiectasis is associated with shortened life span in such patients [29]. 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 subjects [24,25]. In a recent study, Salisbury et al. have compared the survival time and pulmonary function changes of patients with HP and IPF based on the phenotype of radiologic features. HP cases with non-honeycombing fibrosis were found to be associated with longer survival period. Furthermore, HP and IPF patients with honeycombing exhibited poor survival and significant decline in predicted FVC% [33]. In a very interesting study conducted over a 15-year period at the Tokyo Medical and Dental University Hospital, Tateishi et al. defined the HRCT scan 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 [34]. In another population-based single-centric study in China, Wang et al. explored the incidence, clinical characteristics, and outcome of 101 subjects with HP. Interestingly, in contrast to our analysis, the group observed unidentified exposure and low baseline total lung capacity predicted percentage to be independent risk factors as survival predictors in all subjects. Fibrosis on chest HRCT as a clinical variable was not found 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 and clinical features including HRCT patterns and spirometric values of 69 subjects with subacute or chronic HP. It is suggested that the presence of fibrosis on HRCT images and pulmonary function impairment are associated with reduced survival and are indicators of disease prognosis. However, honeycombing independently could not be significantly correlated with mortality [50]. Second, Sahin and colleagues have retrospectively compared HRCT features of HP patients suggestive of fibrosis with scores of histologic fibrosis pattern. They concluded that though HRCT images consisting of extensive reticular, traction bronchiectasis, and honeycomb patterns 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 [51].

The risk factors for only chronic HP patients were also analyzed. The results are in line with our earlier observations for advanced age, honeycombing, and traction bronchiectasis patterns. Our findings are in good agreement with the reports of other research groups where the authors have shown older age [27], honeycombing [19], and traction bronchiectasis [22] features to be associated with high mortality risk of chronic HP patients. The male sex risk factor was found to be statistically significant only for univariate analysis. For multivariate analysis, though this risk factor appeared to be higher, the findings were not significant. This is not surprising given the fact that merely two mortality-related studies are present involving male patients with chronic HP which might have influenced the outcome. In addition, antigen exposure could be significantly associated with the mortality of chronic HP patients. Since prolonged exposure to the sensitized antigen worsens the condition of these patients, antigen avoidance remains the first line of treatment [23].

The present study is not without limitations. First, it is important to mention that we have included one study where risk factor analysis is performed for fibrotic-progression free survival, i.e., the time from diagnosis of HP to fibrotic progression on CT or death, rather than mortality itself. This could have contributed to heterogeneity in the present analysis. Second, all studies included are retrospective in nature with individual observations being clinically different in terms of age, sex, ethnicity, disease severity, and diagnostic procedures. This could also add heterogeneity to our findings despite extensive literature survey, use of well-defined data extraction and quality assessment methods. Third, due to limited reports, we could not perform sub-group analysis of patients with HP based on causative antigens like bird or fungal exposure. An association between the type of antigen and mortality is likely to provide a new direction towards the development of exposure avoidance plans with a patient-centric approach.

A group of patients with HP often report with a family history of DPLD, suggesting predisposed genetic factors. In addition to the clinico-radiological risk factors, it could be useful to identify potential genetic risk factors of the disease. HP often remains undiagnosed due to antigen diversity and lack of standardized methods. With rapid technological advancements, use of multiplexed antigen detection arrays could become an ideal method for accurate identification of causal antigens. In recent years, deep learning has emerged as a promising tool for accurate disease diagnosis with high
sensitivity and specificity since it can efficiently extract meaningful features from high-dimensional clinical and radiological datasets. This approach has demonstrated remarkable progress in precise classification and quantification of HRCT images of complex respiratory diseases. Optimal cutoff values for honeycombing and traction bronchiectasis patterns in HP could be established and used to identify patients with increased risk of mortality.

5. Conclusions
A number of patient characteristics including age, sex, smoking status, FVC, DLCO, antigen exposure, prednisolone therapy, and radiological features including GGO, mosaic attenuation, reticulation, honeycombing, and traction bronchiectasis patterns in patients with HP are analyzed to identify the major risk factors contributing to disease mortality. Out of the various demographic and clinico-radiological factors considered, advanced age, male sex, honeycombing, and traction bronchiectasis emerged to be the most significant risk factors. These mortality-related risk factors of HP can be used to closely monitor patients at a higher risk of disease progression and implement changes early. As evidenced by our findings, elderly male patients having features of honeycombing and traction bronchiectasis require closer monitoring. Interestingly, exposure to causal antigens appeared to be a major mortality-related risk factor for chronic HP. A multicentric observational study is necessary to utilize the present research findings for close monitoring, prognostication, and appropriate management of the disease.

Abbreviations
DLco: Diffusing capacity for carbon monoxide
DPLD: Diffuse parenchymal lung disease
FVC: Forced vital capacity
GGO: Ground glass opacity
HP: Hypersensitivity pneumonia
HRCT: High-resolution computed tomography
IPF: Idiopathic pulmonary fibrosis
OR: Odds ratio

Acknowledgments
S Dasgupta and A Bhattacharya acknowledge the Ministry of Human Resource and Development, India, and Indian Institute of Technology Kharagpur for research fellowship.

Funding
This paper was not funded

Declaration of Interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

Reviewer Disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions
S Dasgupta has full access to all data used in the study and takes responsibility for the integrity and accuracy of the data. S Dasgupta, A. Bhattacharya, and D. Rajwade conducted literature search, extracted the results, performed the meta-analysis, and drafted the manuscript. S Roy Chowdhury and K Chaudhury revised the manuscript.

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Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.

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